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The effectiveness and tolerability of epoetin alfa in patients with multiple myeloma refractory to chemotherapy

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Abstract Anemia is a frequent complication of multiple myeloma, becoming chronic in patients who are resistant to chemotherapy. This randomized, parallel, controlled multicenter study (71 patients receiving concomitant chemotherapy) evaluated the efficacy and safety of epoetin alfa in improving anemia and eliminating the need for transfusions in multiple myeloma patients refractory to conventional first- or second-line chemotherapy. Forty patients were treated with subcutaneous epoetin alfa (150 IU/kg per dose, increasing to 300 IU/kg per dose, every 3 weeks) for 6 months, and 31 entered a control group. The epoetin alfa group had a significantly ($P \leq 0.001$) greater percentage of patients (75% vs. 21%) with increases in hemoglobin levels and/or reduced transfusion requirements. In 44 non pre-transfused patients (20 controls, 24 in the epoetin alfa group), the mean increase in hemoglobin was significantly ($P \leq 0.0001$) greater in the epoetin alfa group (+2.1 vs. –0.2 g/dl). Increases in hematocrit and red blood cells were also significantly ($P \leq 0.0001$) greater in epoetin alfa-treated patients, with corresponding reductions in transfusion requirement. In the 27 pre-transfused patients (11 controls, 16 in the epoetin alfa group), there was a trend towards reduced transfusional need in epoetin alfa-treated patients. Thus, in patients with multiple myeloma refractory to chemotherapy epoetin alfa is a well-tolerated treatment which improves anemia in non pre-transfused patients and appears to reduce transfusion need in those previously transfused.

Key words Epoetin alfa · Anemia · Multiple myeloma · Transfusion · Chemotherapy

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Introduction

Anemia occurs in most cancer patients at some stage and may be related to a variety of factors, such as cachexia, blood loss, and bone marrow involvement. However, one of the major causes is cytotoxic chemotherapy which also frequently aggravates any underlying anemia. Recent studies have estimated that approximately 20% of cancer patients treated with chemotherapy require blood transfusions for anemia [1, 2], and this percentage may be increased markedly with high doses and repeated cycles of treatment [3, 4]. Although virtually all chemotherapeutic drugs have detrimental effects on bone marrow and hematopoietic cells [5, 6], the precise mechanisms of chemotherapy-induced anemia remain to be fully elucidated. It has, however, been proposed that direct effects on the maturation and proliferation of erythropoietin-producing cells may be involved [7]. Endogenous levels of erythropoietin are frequently deficient in patients with anemia related to cancer and chronic diseases such as rheumatoid arthritis, although not in patients with iron deficiency anemia. This effect is known to be intensified by cytotoxic

chemotherapy [7, 8]. Evidence suggests that the nephrotoxic effects of certain chemotherapeutic drugs, such as cisplatin, result in damage to erythropoietin-producing cells [9]. However, the finding that erythropoietin levels in anemic patients were similarly reduced by both cisplatin and non-cisplatin regimens [7], and reports of anemia, sometimes severe, in cisplatin-treated patients without underlying renal failure [9], indicate that other mechanisms are also involved in this blunted erythropoietin response to anemia.

Anemia can have a significant impact on patients' quality of life, due to a wide range of physical symptoms, such as fatigue, weakness, impaired mental function, and respiratory distress. Not only does this contribute to the overall morbidity, but it may necessitate dose reductions, delay or discontinuation of chemotherapy. Transfusions are frequently given in an attempt to manage these effects, although this in turn is associated with a number of risks, including allergic reactions, iron overload, immune suppression, and infection.

Multiple myeloma is a progressive lymphoid malignancy characterized by the proliferation of a single clone of plasma cells which produce a structurally homogeneous immunoglobulin. Clinical symptoms include osteolytic lesions, renal damage, bacterial infections, and anemia, which represents a common complication as the malignant plasma cells invade the bone marrow [10]. The myeloma-related anemia is generally moderate, although in some cases it may be severe, and tends to become more frequent with the progression and duration of the neoplasia. A number of conditions contribute to the occurrence of anemia, including reduced production of erythroblasts, a decrease in erythropoietin secondary to renal failure, and production of a number of cytokines, such as interleukin-6. Although complete remission following chemotherapy generally resolves anemia, this can be expected in only about 10% of patients [11]. In contrast, the majority of patients achieve a temporary response or are non-responders, and consequently the anemia persists and becomes chronic.

Studies with epoetin alfa (recombinant human erythropoietin) in anemic patients with a variety of hematological and solid malignancies have resulted in increased hemoglobin levels and hematocrit, and reduced transfusion requirements [12–17]. These promising findings have been reiterated in a number of studies specifically investigating anemia associated with multiple myeloma, with increases in hemoglobin levels ≥2 g/dl or hematocrit ≥6% reported in at least 70% of patients [18–21]. The objective of the present study was to investigate the safety and efficacy of subcutaneous epoetin alfa in improving anemia and eliminating the need for transfusion in patients with multiple myeloma resistant to conventional first- and second-line chemotherapy. The effect of epoetin alfa therapy on the progression of the lymphoproliferative disease was also examined.

Materials and methods

Study design and treatment

This open-label, randomized, parallel-group, controlled, multicenter study was conducted over a 6-month period in patients with anemia and symptomatic multiple myeloma refractory to conventional chemotherapy. Treatment with chemotherapy could be continued throughout the study and was accompanied by local radiotherapy in the case of painful local bone lesions.

Epoetin alfa (Eprex) was initiated at a dose of 150 IU/kg administered subcutaneously three times per week. Patients were re-evaluated periodically throughout the study and the dosage of epoetin alfa was increased to a maximum of 300 IU/kg per dose in patiens who did not experience an increase in hemoglobin level and/or reduction in transfusion requirements. The dosage was also adjusted to maintain hemoglobin levels between 12 and 14 g/dl. Oral iron supplementation (200 mg/day elemental iron) was administered in cases where serum ferritin concentrations fell below 100 mg/ml, and transfusions were administered if hemoglobin levels fell below 7 g/dl or if the patient had cardiovascular symptoms or severe asthenia. In addition to treatment with conventional chemotherapy (with or without radiotherapy), all other concomitant therapies were recorded throughout the study.

Patients

Anemic male and female patients with a confirmed diagnosis of multiple myeloma (Durie-Salmon stage II or IIIa) resistant to first-line (at least 12 months of standard first-line therapy) or second-line (relapsed patients refractory to rescue therapy) conventional chemotherapy, and with a stable serum/urinary monoclonal (M) component during the previous 3 months, were eligible for inclusion. Patients were required to have anemia (hemoglobin level <10 g/dl) for at least the preceding 3 months and/or transfusion dependence (at least 2 transfusions in the previous month). Exclusion criteria comprised multiple myeloma previously untreated with chemotherapy, relapse never treated with rescue chemotherapy, severe renal failure (creatinine >2 mg/dl or requirement for dialysis), hypertension (diastolic blood pressure >100 mmHg), anemia due to hemolytic autoimmune disease or deficiency of folate, vitamin B_{12}, or iron, concomitant disease and/or severe physiological dysfunction not attributable to the typical pathology of multiple myeloma, a Karnofsky performance status score of <40% or a poor general condition, concomitant treatment with other growth factors, or participation in another clinical trial. During analysis of the data, it became clear that 2 enrolled patients did not fulfil these criteria and should have been excluded.

A total of 71 patients from 12 centers were enrolled in the study and randomized to the control group ($n=31$) or to treatment with epoetin alfa ($n=40$). Patients were also stratified according to their transfusion requirements in the 4 weeks prior to the start of the study as either not pre-transfused ($n=24$ in the epoetin alfa group and 20 in the control group) or pre-transfused ($n=16$ in the epoetin alfa group and 11 in the control group). Pre-transfusion was defined as the transfusion of at least 1 blood unit over the 4 weeks preceding the start of the study. The demographic and baseline characteristics are summarized in Table 1. No significant differences were detected between the two patient groups.

The study was performed in accordance with the Declaration of Helsinki (1964), revised in Tokyo (1975), and the subsequent Venice (1983) and Hong Kong (1989) amendments. Approval of the protocol was obtained from the ethical review committees of centers participating in the trial and all patients gave their informed consent.

Study procedures

Baseline assessments included a physical examination and medical history, Karnofsky performance status, hematological analyses (hemoglobin, hematocrit, complete blood count, reticulocyte count), vi-

Table 1 Demographic and baseline characteristics

	Control (n=31)	Epoetin alfa (n=40)	Total (n=71)
Male/female (n)	15/16	20/20	35/36
Mean age (years)±SD (range)	65.0±8.8 (47–85)	60.6±8.3 (39–74)	62.5±8.8 (39–85)
Median duration of myeloma (years) (range)	2.3 (0.2–7.0)[a]	2.1 (0.2–14.3)	2.2 (0.2–14.3)[a]
Stage of myeloma: II/III a/not reported (n)	8/23/0	11/28/1	19/51/1
Bone lesions: present/absent (n)	27/4	28/12	55/16
Pre-transfused: yes/no (n)	11/20	16/24	27/44
Karnofsy performance status (n)			
<40%	1	0	1
40%	5	7	12
50–60%	5	9	14
70–80%	14	13	27
90–100%	3	6	9
not reported	3	5	8
Bone marrow plasmacytes (n)			
0–10%	1	6	7
11–30%	6	6	12
31–50%	8	10	18
51–70%	5	7	12
71–90%	3	3	6
>90%	0	2	2
not reported	8	6	14
Monoclonal Ig class: G/A/not reported (n)	21/6/4	35/3/2	56/9/6

[a] Not reported in 1 patient

tal signs, body weight, serum/urinary M component, bone marrow aspirate, ECG, chest X-ray a direct Coombs' test, and haptoglobin evaluation. Vital signs and any adverse events were recorded after each dose of epoetin alfa. Hemoglobin and hematocrit were measured every week during the first 2 months of the study and then every other week for the remaining 4 months; there were also monthly hematology assessments (hemoglobin, hematocrit, complete and differential count, reticulocytes, platelets), blood chemistry, and evaluation of the stage and possible progression of the disease based on the M component. Final evaluations after completion or early termination of the study included a physical examination, information regarding premature discontinuations, ECG, determination of Karnofsky performance status, hematology, blood chemistry, bone marrow aspiration, degree of bone marrow infiltration, and serum/urinary M component.

Statistical analysis

The data were analyzed based both on randomization to the control or epoetin alfa group and according to whether patients were pre-transfused or not. Hemoglobin levels in the two treatment groups were compared according to an intention-to-treat principle using an analysis of covariance (ANCOVA). The baseline hemoglobin was used as a covariate, taking the last value observed during the trial as the final hemoglobin value, irrespective of the actual treatment duration and of possible intercurrent transfusions. The last pre-transfusional value during the study period was taken as the final hemoglobin value and compared, again, with baseline hemoglobin as a covariate in ANCOVA analysis.

A full response for non-transfused patients was defined as ≥2 g/dl hemoglobin increase within the 24-week study period, whereas an increase of <2 g/dl hemoglobin in a similar period was considered as a partial response. Hematocrit and red blood cells were analyzed as further parameters by the same method described for hemoglobin, while the number of blood units given was compared using the Mann-Whitney U test. In pre-transfused patients a parameter was the number of units transfused between week 4 and the end of the study. Repeated analyses were performed using the Mann-Whitney U test which compared the number of units transfused over 4-week periods throughout the study. The level of significance for each test was set at 0.01 in order to preserve an overall type 1 error risk of 0.05. Baseline values were based on the number of units transfused during the 4 weeks before and the 4 weeks after the start of the study. In pre-transfused patients, the hemoglobin levels immediately prior to transfusion were compared between the treatment groups using an unpaired t-test, whereas an interruption of transfusional need for at least 8 weeks was defined as a full response. In contrast, an interruption for 4 weeks was regarded as a partial response.

Table 2 Analysis of overall hematological response in all enrolled patients

	Control (n=31)	Epoetin alfa (n=40)
Not assessed	2	4
Non-responder	23 (79.3%)	9 (25.0%)
Partial responder	3 (10.3%)	11 (30.6%)
Full responder	3 (10.3%)	16 (44.4%)
	$P \leq 0.001$[a]	

[a] Mantel-Haenszel chi-squared test

The percentage of patients who experienced increased hemoglobin levels and/or reduced requirements for transfusion, and change in Karnofsky performance status, were both secondary efficacy parameters. The level of clinical response (the change in hemoglobin level for non pre-transfused patients and the number of transfusions for the pre-transfused group) in each patient was assessed blindly and independently by two or three individuals, and the percentage of responders in each treatment group was compared using the Mantel-Haenszel chi-squared test (Table 2). Changes in the Karnofsky status were compared within treatment groups using the Wilcoxon's one-sample signed rank-sum test and between treatment groups using the Mann-Whitney U test. All tests were two-sided and carried out at the 0.05 significance level, except for the repeated analyses.

Safety assessments included the type, severity, and duration of adverse events elicited by non-direct questioning, vital signs, and laboratory tests. Time changes of blood pressure and heart rate in patients who completed the 24-week trial were tested by performing an analysis of variance within each treatment group.

Results

Distribution of myeloma patients and administration of the drug

Of the 71 patients enrolled in the study, 27 (11 controls and 16 in the epoetin alfa group) were pre-transfused and 44 (20 controls and 24 in the epoetin alfa group) were not pre-transfused. A total of 22 patients (7 controls and 15 in the epoetin alfa group) discontinued treatment before the end of the study; the reasons are shown in Table 3. Eighteen patients (7 controls and 11 in the epoetin alfa group) violated the protocol, since they did not meet the inclusion/exclusion criteria, or were apparently not correctly randomized. A further 2 patients, 1 from each group, with a recently diagnosed (2.5 months) multiple myeloma (stage

Table 3 Reasons for premature discontinuation

	Control	Epoetin alfa
Death[a]	5	9
Lost to follow-up	2	2
Disease progression	0	1
Disease remission	0	1
Surgery	0	1
Not specified	0	1
Total	7	15

[a] Deaths were due to infectious/renal/respiratory complications (7) or disease progression (2) in the epoetin alfa group and renal or cardiovascular complications (4) or disease progression (1) in the control group

Table 4 Transfusion requirements in non pre-transfused patients (all patients enrolled), by treatment group

	Control ($n=20$)	Epoetin alfa ($n=24$)	P
Mean (range) time to final determination of hemoglobin (weeks)	21.6 (1.0–26.3)	18.9 (1.9–25.3)	0.2
Number of patients transfused	9 (45%)	6 (25%)	0.2
Mean (range) number of blood units transfused	2.5 (0–19)	1.2 (0–16)	0.1

IIIA) were erroneously enrolled. Both patients were pre-transfused and continued chemotherapy (melphalan with prednisolone) during the trial. The patient in the control group, a 69-year-old female with a baseline hemoglobin of 6.5 g/dl which increased to 7.1 g/dl, died after 2 weeks due to heart failure. This patient also failed to meet the inclusion criterion of having a Karnofsky performance status of at least 40% (Table 1). The patient in the treatment group, a 63-year-old male, responded with an increase of hemoglobin from 8.1 g/dl to 14.5 g/dl by week 16, without any transfusion or disease progression until the end of the expected 6 months of observation.

Epoetin alfa treatment was temporarily suspended in 8 patients because of renal failure with or without hypertension (2), attainment of satisfactory hemoglobin values (2), patient request (2), varicella infection (1), and concomitant administration of immunomodulating agents (1). Modifications of epoetin alfa dose were generally related to hemoglobin changes in response to treatment.

Concurrent chemotherapy was administered to 26 patients in the control group and 35 in the epoetin alfa group. The most-common regimens included melphalan and cyclophosphamide, given either alone or in combination with vincristine ($n=36$). Other chemotherapeutic agents used included epirubicin, doxorubicin, etoposide, teniposide, cisplatin, carmustine, chlorambucil, and cytarabine. Corticosteroids were administered to 25 control patients and 34 epoetin alfa patients, mainly in combination with chemotherapy. Prednisolone or methylprednisolone were used most frequently, either alone ($n=35$) or in combination with the dexamethasone or deflazacort ($n=7$). Other regimens included single-agent treatment with dexamethasone ($n=8$), deflazacort ($n=6$), or betamethasone ($n=3$). Iron supplements were required by 2 patients in the control group and 3 in the epoetin alfa group.

Transfusion requirements and hematological responses

Treatment with epoetin alfa showed benefits in terms of transfusion requirements and hematological responses. As shown in Table 4, 6 of the non pre-transfused patients (25%) in the epoetin alfa group required transfusion during the study compared with 9 (45%) in the control group; this difference was not statistically significant ($P=0.23$). In addition, the mean number of blood units transfused during the study in the epoetin alfa group was approximately half that transfused in the control group (1.2 vs. 2.5), although the difference did not achieve statistical significance ($P=0.12$). The mean hemoglobin level before transfusions was 7.5 g/dl in the control group and 8.4 g/dl in the epoetin alfa group. Statistically significant differences between the treatment groups were observed in hematological responses with epoetin alfa, resulting in significantly greater ($P\leq0.0001$) mean increases from baseline to endpoint in hemoglobin (+2.09 g/dl vs. −0.17 g/dl), hematocrit (+8.0% vs. −0.4%), and red blood cells ($+0.83\times10^6$/mm^3 vs. $+0.01\times10^6$/mm^3) compared with the control group. There were no differences between the treatment groups at baseline for any of these hematological parameters. The hematological responses in all enrolled non pre-transfused patients are shown in Table 5. These findings were confirmed in sub-analyses of all eligible patients who completed the study. There was also a highly significant difference ($P=0.0027$) in hemoglobin levels between both treatment groups when any possible contribution of transfusions during the study period was excluded (Table 6).

In contrast to the non pre-transfused patients, analysis of pre-transfused patients revealed statistically significant ($P\leq0.02$) differences between the two treatment groups at baseline, with the control group receiving more mean units of blood (4.0 vs 2.6) and having a higher mean hemoglobin value at initiation of transfusion (8.3 g/dl vs. 7.4 g/dl) in the 4 weeks prior to the start of the study. This difference occurred despite stratification of transfusion requirements during randomization, and must be taken into consideration when directly comparing the control and epoetin alfa groups. Nonetheless, the number of blood units transfused per patient and per 4-week interval was calculated and progressively cumulated between the 5th week and the end of the study. There was a marked trend towards reduced requirement for transfusion in patients treated with epoetin alfa compared with controls. Figure 1 shows the mean number of blood units transfused in each treatment group over 4-week intervals throughout the study. A comparison of the mean number of blood units transfused in the control and epoetin alfa groups between week 5 and 16 (2.17 vs. 1.01, $P=0.065$), week 5 and 20 (2.56 vs. 0.71, $P=0.018$), and week 5 and the end of the

Table 5 Hematological response in non pre-transfused patients by treatment group

		Control ($n=20$)	Epoetin alfa ($n=24$)	P^a
Mean (±SD) hemoglobin (g/dl)	Baseline	8.34±1.4	8.67±0.9	
	Endpoint	8.17±1.7	10.76±2.0	
	Change	0.17±1.5	+2.09±1.7	0.0001
Mean (±SD) hematocrit (%)[a]	Baseline	25.8±4.8	26.0±3.5	
	Endpoint	25.4±5.9	34.0±7.1	
	Change	−0.4±2.7	+8.0±6.2	0.0001
Mean (±SD) red blood cells ($10^6/mm^3$)[b]	Baseline	2.79±0.6	2.81±0.5	
	Endpoint	2.80±0.6	3.64±0.8	
	Change	+0.01±0.5	+0.83±0.6	0.0001

[a] Analysis of covariance (ANCOVA) on final values with baseline values as covariate
[b] 1 control and 5 epoetin alfa observations were missing for hematocrit and red blood cell determinations

Table 6 Change in hemoglobin level in non pre-transfused patients by treatment group to study end or first mid-study

			Control ($n=20$)	Epoetin alfa ($n=24$)	P
Hemoglobin (g/dl)	Mean±SD	Baseline	8.34±1.4	8.67±0.9	
		Final	7.84±1.7	10.03±2.5	
		Change	−0.50±1.6	+1.35±2.0	0.0027*
Time to final hemoglobin determination (weeks)	Mean		16.0	15.8	0.93**
	Min-max		1.0–26.3	0.9–24.4	

* ANCOVA on final values with baseline values as a covariate
** Wilcoxon's two-sample rank-sum test

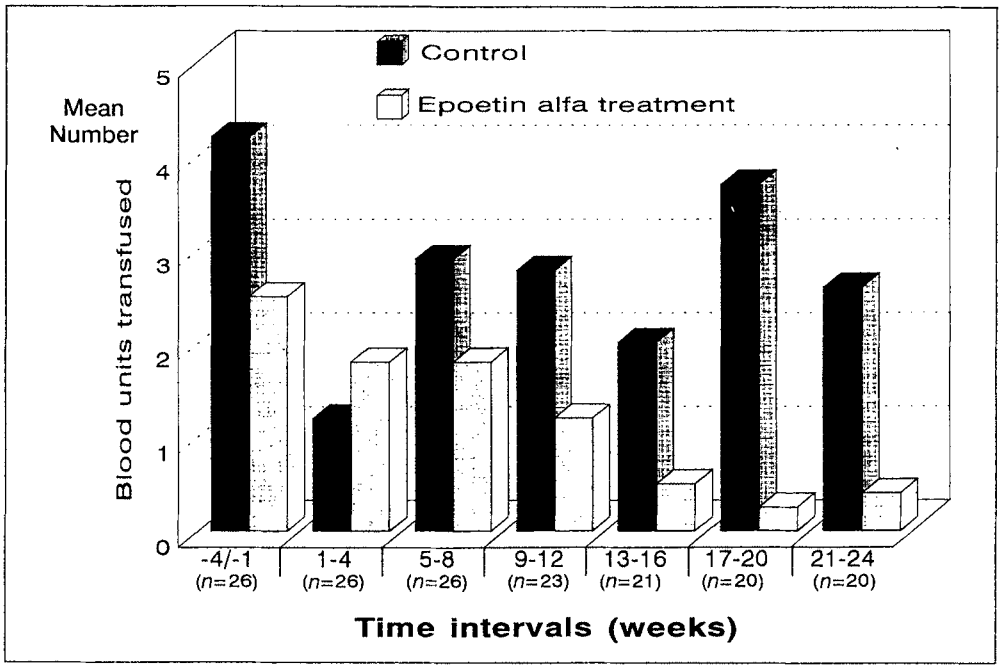

Fig. 1 Mean number of blood units transfused over 4-week intervals throughout the study in pre-transfused patients, by treatment group

study (2.57 vs. 0.64, $P=0.013$) revealed lower transfusion requirements with epoetin alfa in each period. Significance was conservatively set at $P=0.01$. Similar comparisons of the mean hemoglobin level in each treatment group at initiation of transfusion between week 1 and 4, and between week 5 and 24 did not reveal any significant differences.

Overall clinical response

When clinical response was blindly evaluated in all patients, the overall percentage of patients showing a full or partial response, in terms of increase in hemoglobin level or a decrease in transfusion requirements, was significantly greater in the epoetin alfa than in the control group (75%

Table 7 All adverse events reported throughout the study by treatment group (reported by 8 control patients and 14 epoetin alfa-treated patients)

	Control ($n=31$)	Epoetin alfa ($n=40$)
Renal insufficiency	2	5
Cardiovascular complications	4	1
Hypertension/aggravation of hypertension	0	5
Respiratory tract infection	1	4
Progression of multiple myeloma	1	3
Fever	0	2
Oral candidiasis	0	2
Sweating	1	0
Pruritus	1	0
Gastralgia	0	1
Asthenia	0	1
Pleural effusion	0	1
Varicella	0	1
Infection (other)	0	1
Acute myeloid leukemia	0	1

vs. 21%, $P \leq 0.001$). Response was not assessed in 2 control and 4 patients in the epoetin alfa groups, respectively. This result was confirmed in a sub-analysis of eligible patients only.

Karnofsky performance status

Approximately 25% of patients had no final measure of Karnofsky performance status, mostly due to the difficulty of determining the performance status of patients who discontinued the trial. Thus, the value of this assessment is limited. However, of the patients who could be assessed, there were no statistically significant differences between the control and epoetin alfa groups at baseline, 12 weeks, or 24 weeks, when assessed overall, or by transfusion requirement before the study. Comparison of values at 24 weeks with baseline also did not reach statistical significance, except for control patients overall, whose performance status worsened significantly ($P=0.03$). Progression or complications of multiple myeloma and death were responsible for most of the observed changes.

Safety and tolerability

Treatment with epoetin alfa was generally well tolerated; adverse events were reported by 14 of 40 (35%) epoetin alfa-treated patients compared with 8 of 31 (26%) in the control group. Table 7 shows all adverse events reported throughout the study in both groups. Cardiovascular complications and renal damage were the most common events in the control group, while patients in the epoetin alfa group experienced hypertension and kidney failure frequently. Multiple myeloma progressed in 3 epoetin alfa-treated patients and 1 control patient, since these patients were refractory to first- and second-line chemotherapy.

The only adverse event that appeared to be specific to the epoetin alfa group was hypertension. Increases in both systolic and diastolic blood pressure were reported in 5 patients and were considered likely to be related to treatment in 3 of these cases. However, control was easily achieved with antihypertensive therapy. Interestingly, hypertension occurred in all but 1 patient who responded to epoetin alfa with a marked increase in hemoglobin. No clinically significant changes of heart rate, respiratory rate, or body temperature related to the study treatment were observed.

There were 5 (16%) deaths in the control group and 9 (23%) in the epoetin group, none of which were causally related to treatment. Progression of multiple myeloma occurred in 4 patients, 1 in the control group and 3 in the epoetin alfa group. Respiratory tract infections, including bronchopneumonia and pleural involvement, occurred in 7 patients, 6 in the epoetin alfa group and 1 in the control group. Oral candidiasis was observed in 2 patients treated with epoetin alfa. In none of these cases were the infectious events judged to be related to treatment. Renal damage was reported and abnormal creatinine levels were detected in 10 patients (6 receiving epoetin alfa and 4 in the control group). No other clinically significant abnormalities of laboratory data in individual patients were observed during the study, except for those related to the underlying disease or its complications.

Discussion

Multiple myeloma is frequently accompanied by chronic anemia in chemotherapy-resistant patients. Current treatment involves regular blood transfusions, which themselves are associated with a variety of problems. The results of this 6-month controlled study suggest that subcutaneous epoetin alfa (150 IU/kg per dose initially) administered three times per week may provide a safe and effective alternative, or adjuvant, to transfusion in this patient population. Although definitive conclusions could be drawn only in non pre-transfused patients, there was an overall reduction in transfusion requirements during epoetin alfa therapy. Moreover, the overall percentage of patients showing a substantial increase in hemoglobin level or a decrease in transfusion requirements in response to treatment was significantly greater in the epoetin alfa group than in controls (75% vs. 2%, $P \leq 0.001$). Similar, or even higher, percentages of response to epoetin alfa therapy have been observed in a number of previous studies in anemic patients with multiple myeloma (75%–85%) [18, 20, 21]. It has been suggested that tubular nephropathies in multiple myeloma patients may impair the secretion of endogenous erythropoietin [22]. In this situation, exogenous administration of erythropoietin can sufficiently increase concentrations to stimulate erythropoiesis.

In the non pre-transfused group of patients presented here, transfusions were required by a considerably lower percentage of epoetin alfa-treated patients compared with controls (25% vs. 45%) and the mean number of blood units transfused was less than half that employed in the control group. This marked reduction was accompanied

by significant increases in hemoglobin, hematocrit, and red blood cells compared with the control group ($P \leq 0.0001$). Although slight reductions in hemoglobin and hematocrit were observed in the control group, red blood cell levels were virtually unchanged. Indeed, for all three parameters, the difference between the change from baseline to endpoint in the epoetin alfa group and the control group was statistically significant (Table 5). A significant change in the hemoglobin level in both treatment groups was also observed after exclusion of any possible mid-study transfusion influence (Table 6). These results suggest that epoetin alfa is effective not only in improving anemia, but may also prevent the need for transfusion in some patients.

Evaluation of efficacy was more problematic in the group of pre-transfused patients, due to differences in baseline transfusion practices and the smaller number of patients enrolled. These effects highlighted the difficulties associated with conducting an open-label trial. Nevertheless, there was a trend towards reduced transfusional requirements in epoetin alfa-treated patients compared with controls, from week 5 to the end of the study. A clear benefit could not be observed during the first 4 weeks of epoetin alfa therapy (part of the defined baseline period), but this is most likely due to the hormone's pharmacodynamic properties and the fact that it usually takes 4–6 weeks to stimulate erythroid precursor cells (BFU-E) in the bone marrow.

Although quality of life was not measured in this study, the results of other studies suggest it would have been interesting to monitor this aspect. Improvements in parameters such as energy level, ability to perform daily activities, and overall quality of life have been reported in several trials in patients experiencing hematological responses to epoetin alfa [14, 15, 23–26].

Only 4 patients showed progression of multiple myeloma during the study, with no observed differences between the treatment and control groups, and changes in the Karnofsky performance status appeared to be related to the progression of the disease, or complications arising from it, rather than the anemia or the administration of transfusions.

Epoetin alfa was generally well tolerated. Adverse effects occurred in a similar number of patients in each group and the only event which appeared to be specifically related to epoetin alfa therapy was hypertension, but in 3 patients it was easily controlled by antihypertensive therapy. However, increases in blood pressure are a recognized drug-related effect in uremic patients, so it is not surprising to find some cases among patients with multiple myeloma. It has also been suggested that hypertension could be associated with a rapid rise in hematocrit. Interestingly, in the current study hypertension occurred in all but 1 patient who responded to epoetin alfa with a marked increase in hemoglobin.

In conclusion, the results of this study in patients with multiple myeloma resistant to chemotherapy indicate that epoetin alfa is a safe treatment which improves anemia and reduces or prevents transfusion requirements in patients not previously transfused. Evidence also suggests that epoetin alfa at a dosage of 150 IU/kg three times a week may reduce the transfusion requirement in those who have already received prior transfusions.

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