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Efficacy of epoetin alfa in the treatment of anaemia of multiple myeloma

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Summary. Effects of epoetin alfa on transfusions, haemoglobin (Hb) and quality of life (QOL) were evaluated in a placebo-controlled study of 145 patients with multiple myeloma and anaemia (Hb < 11 g/dl). During the 12-week, double-blind phase, patients received 150 IU/kg epoetin alfa or a matching volume of placebo subcutaneously three times weekly; the dose (or volume) was doubled at week 4 if Hb response was inadequate. Patients completing this phase could enter the subsequent optional 12-week phase of open-label epoetin alfa treatment. During double-blind treatment, epoetin alfa significantly decreased the incidence of transfusion compared with placebo (28% vs. 47%, $P = 0{\cdot}017$), regardless of patients' transfusion history, and increased mean Hb (1·8 g/dl vs. 0·0 g/dl, $P < 0{\cdot}001$). Univariate analysis showed significant ($P \leq 0{\cdot}05$) improvement in more QOL measures with epoetin alfa than with placebo; multivariate analysis discerned no between-treatment differences. Significantly ($P = 0{\cdot}038$) more epoetin alfa vs. placebo patients had improved performance scores. At the end of the open-label treatment phase, patients who had continued epoetin alfa maintained Hb status, and placebo patients who were switched to epoetin alfa had mean Hb increases of 2·4 g/dl. Adverse events were similar between treatment groups. Epoetin alfa proved effective and well tolerated for treating anaemia in patients with multiple myeloma.

Keywords: multiple myeloma, anaemia, epoetin alfa, cancer, quality of life.

Multiple myeloma is a malignant plasma cell neoplasm, the incidence of which increases with increasing age (Turesson *et al*, 1984; Hjorth *et al*, 1992). Anaemia has been reported in up to 70% of patients with multiple myeloma (Kyle, 1975; Riccardi *et al*, 1991; Garton *et al*, 1995), often caused by the inadequate production of erythropoietin (Beguin, 1995). Additional factors contributing to anaemia in multiple myeloma patients may include bone marrow infiltration by malignant cells, reduced survival of red blood cells (RBCs), chronic renal insufficiency, cytokine production and the myelosuppressive effects of chemotherapy. Anaemia can result in fatigue, exhaustion, dizziness, depressed mood, impaired cognitive function, respiratory distress, cardiac decompensation and other symptoms that impair function and diminish patient quality of life (QOL) (Winningham *et al*, 1994; Cella, 1998; Ludwig & Fritz, 1998; Schwartz, 1998).

In most patients with multiple myeloma, anaemia improves when the disease responds to chemotherapy (San Miguel *et al*, 1999). In cases where this does not occur or chemotherapy is not required, treatment options for anaemia are blood transfusions or the administration of recombinant human erythropoietin (rHuEPO, epoetin alfa). Blood transfusions are associated with several serious, albeit infrequent, risks (e.g. allergic reactions, infection, iron overload), and epoetin alfa is thus an appealing alternative (Ludwig & Fritz, 1998; Goodnough *et al*, 1999). A glycoprotein hormone, epoetin alfa increases the production of RBCs by stimulating the expansion of erythroid progenitor cells and decreasing apoptosis of erythroid burst-forming unit cells and granulocyte colony-forming unit cells (San Miguel *et al*, 1999). Clinical studies have demonstrated that epoetin alfa can prevent or ameliorate anaemia and reduce transfusion requirements in anaemic patients with a variety of cancers, including multiple myeloma (Ludwig *et al*, 1990, 1993; Abels, 1992; Barlogie & Beck, 1993; Leitgeb *et al*, 1994; Dunphy *et al*, 1997; Mittelman *et al*, 1997; Musto *et al*, 1997; Dammacco *et al*, 1998). Furthermore, several studies with a combined total of nearly 5000 evaluable patients have shown that correction of anaemia with epoetin alfa can improve the QOL in patients with cancer

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(Ludwig *et al*, 1990; Abels, 1992; Leitgeb *et al*, 1994; Glaspy *et al*, 1997; Mittelman *et al*, 1997; Demetri *et al*, 1998).

The study presented here evaluated the efficacy of epoetin alfa in correcting anaemia in patients with multiple myeloma, thereby decreasing transfusion requirements. Additionally, patients were monitored for changes in haemoglobin (Hb) levels and in performance status and improvements in QOL.

PATIENTS AND METHODS

Patients. Men and women aged 40–80 years with multiple myeloma, a life expectancy of at least 3 months and an Eastern Cooperative Oncology Group (ECOG) score of 0–3 were eligible for the study. Patients must have been receiving chemotherapy for at least 6 months and had to have a baseline Hb level $< 11{\cdot}0$ g/dl. Patients with uncontrolled hypertension or evidence of untreated iron, folate or vitamin B_{12} deficiency were excluded, as were those who had received a blood transfusion within 7 d of study entry. Also excluded were patients who had a major infection within 1 month, or an acute illness within 7 d, of study entry.

Study design and treatment. The multicentre, randomized trial began with a 12-week, double-blind, placebo-controlled treatment phase, which was followed by a 12-week, open-label extension phase. Patients who entered the study were stratified according to receipt of blood transfusion within the preceding 3 months. Patients within each transfusion stratum were then assigned randomly to receive epoetin alfa (marketed in Europe as EPREX/ERYPO, Janssen-Cilag and Ortho Biotech Europe, and in the USA as PROCRIT, Ortho Biotech Products, LP) 150 IU/kg or a matching volume of placebo. Study drug was administered subcutaneously three times weekly (t.i.w.) for 12 weeks, with each dose separated by at least 1 d; this dosage was continued if the Hb level increased by ≥ 1 g/dl within 4 weeks of treatment.

Dosage could be modified during treatment. If the Hb level:

- had not increased by ≥ 1 g/dl after 4 weeks of treatment, the dose was doubled to 300 IU/kg t.i.w. (or the volume of placebo was doubled) for the remaining 8 weeks of the study;
- increased to > 14 g/dl at any time during the study, study drug was withheld until the Hb level was < 12 g/dl and then reinitiated at a dose approximately 25% lower than that administered previously;
- increased by 2 g/dl or more within a 4-week period, the dose was reduced by approximately 25% to maintain an increase of < 2 g/dl/month.

Study drug was blinded for identity (epoetin alfa or placebo), but not for dose level (150 or 300 IU/kg). Transfusions were permitted but were to be avoided, if possible, in patients with Hb levels > 8 g/dl.

The following physical evaluations were completed 7 d prior to study entry, on day 1 preceding administration of study drug and weekly during the double-blind phase: vital signs; clinical laboratory tests including complete blood count and reticulocyte count; serum chemistry; and urinalysis. Serum erythropoietin level was evaluated prior to study entry, on day 1 and at weeks 2, 4 and 8. Serum iron, transferrin, total iron-binding capacity and ferritin were evaluated prior to study entry, on day 1 and every 4 weeks. Additional procedures conducted prestudy, at the end of the double-blind phase and at completion of the open-label phase were complete physical examination, assessment of the clinical signs and symptoms of multiple myeloma, bone marrow biopsy, skeletal radiography, serum M-component, urine light-chain M-component, folate, B_{12}, myeloma staging, and physician's performance score and global assessment.

Both epoetin alfa- and placebo-treated patients who completed the 12-week, double-blind phase had the option of receiving epoetin alfa for up to 12 weeks in the open-label extension phase of the study. Patients who had received epoetin alfa continued at the same dosage as their final dose during double-blind treatment. Patients who had received placebo were administered epoetin alfa 150 IU/kg t.i.w., which could be titrated up to 300 IU/kg t.i.w. as in the double-blind phase of the study. The evaluation procedures noted above were completed every 4 weeks for patients who continued receiving epoetin alfa, and on the same schedule as in the double-blind phase for patients who had received placebo and crossed over to epoetin alfa.

Evaluation of efficacy and safety. The primary efficacy evaluation was transfusion requirements stratified by baseline transfusion status. Secondary measures of efficacy were: (1) changes in Hb from baseline to last determination; (2) the proportion of patients who, at any time during the double-blind phase, had an increase of at least 2 g/dl in Hb level (responders) or who achieved an Hb level of at least 12 g/dl (correctors) without receiving a transfusion within the preceding month; (3) changes in QOL scales; and (4) global assessment and changes in physician-rated ECOG performance scores.

The effects of epoetin alfa on QOL were measured using two questionnaires: the Nottingham Health Profile (NHP) (Hunt & McKenna, 1989) and the Cancer Linear Analogue Scale [CLAS, also known as the Linear Analogue Scale Assessment (LASA)]. The NHP is an instrument comprising 38 questions that can be combined to form six separate QOL scales: Emotional Reactions, Pain, Energy, Sleep, Social Isolation and Physical Mobility. Examples of the questions include: 'The day seems to drag', 'I sleep badly at night', 'I feel lonely' and 'I find it hard to dress myself'. Patients respond to the NHP questions as *yes* or *no*. Scale scores are calculated by counting the number of items within each scale rated as a *yes*. This scale is then converted to a scale of 0 (good) to 100 (bad), using the following formula: scale score = (number of yes answers) $\times$ (100 $\div$ number of items in the individual scale). Lower values represent better responses. The CLAS is a horizontal 100-mm scale that separately evaluates energy level, ability to do daily activities and overall QOL. The left extreme of the scale (0) represents the worst or lowest possible score, and the right extreme (100) represents the best or highest possible score. Patients mark how they feel within these extremes. The NHP and

CLAS were completed by patients before the start of study medication on day 1 and at the end of weeks 4, 8 and 12 of the double-blind phase. During the open-label phase, the questionnaires were again completed at weeks 4, 8 and 12; however, the initial (day 1) assessment was based on the week-12 (end of study) evaluation from the double-blind phase.

Change in ECOG performance score was rated by the physician using a scale with values that ranged from 0 = able to carry out all normal activities without restriction to 4 = completely disabled, cannot carry out any self-care and totally confined to bed or a chair. Also, the physician rated the effect of study medication (epoetin alfa or placebo) globally, using values of 1 = poor to 5 = excellent.

Safety was evaluated by questioning patients at each study visit about adverse events. All adverse events, as well as the investigator's assessment of its seriousness, severity and presumed relationship to study medication, were recorded.

Statistical analysis. Results for the primary efficacy evaluation of transfusion requirements and safety are reported for the intention-to-treat (ITT) population (all patients randomized to a treatment group). The proportion of patients transfused stratified by prestudy transfusion history was analysed by the Cochran–Mantel–Haenszel test. Only data for months 2 and 3 were analysed, as treatment effects were not expected before this time (Abels, 1992).

Results for the secondary efficacy parameters are reported for patients randomized to a treatment group who remained in the study for at least 2 months (56 d) [efficacy (EFF) population]. It was believed that this duration would allow patients, including those who required a dose increase at week 4, sufficient time to respond. Between-group changes in haematological parameters from baseline to last determination were compared using *t*-tests; between-group differences in the proportions of responders and correctors were compared using the Fisher exact test.

Quality of life analyses were performed for the ITT population minus patients who died during the double-blind phase of the study and did not have final QOL data. To ensure that no bias was introduced by deleting patients who died, Kruskal–Wallis tests were performed (Stronks *et al*, 1995). Quality of life assessments were evaluated by univariate analyses using *t*-tests; multivariate analyses were also performed. Change in performance scores between the treatment groups, categories of response to chemotherapy and the treatment groups stratified by response to chemotherapy were analysed using Kruskal–Wallis and Cochran–Mantel–Haenszel tests. Between-group differences in the physician's global assessment were analysed by the Kruskal–Wallis test. All statistical tests were two-sided.

RESULTS

Patients

The ITT group comprised 145 patients (69 epoetin alfa and 76 placebo) enrolled at 31 sites in 12 countries (Italy, Poland, Great Britain, Norway, Sweden, Czech Republic, Hungary, Belgium, Israel, Denmark. Spain and Switzerland). Baseline demographic and clinical characteristics were comparable between treatment groups (Table I). Approximately one-third of patients in the epoetin alfa (36·2%) and placebo (36·8%) groups had received a transfusion during the 3 months before study entry; baseline Hb levels for those patients were comparable. The most commonly used chemotherapeutic agents were melphalan, vincristine, cyclophosphamide and doxorubicin, often with concomitant prednisone or dexamethasone.

After 4 weeks of treatment, the dose of study medication was increased to 300 IU/kg t.i.w. for 24/67 (35·8%)

Table I. Baseline demographics and clinical characteristics.

Characteristic	Epoetin alfa (n = 69)	Placebo (n = 76)
Gender (%)		
Female	51	59
Male	49	41
Age (years)		
Median	67·3	65·0
Range	43·0–80·4	38·2–88·9
Creatinine (μmol/l) mean	106·3 ± 42·29	102·4 ± 35·60
No. of chemotherapy cycles within 6 months prestudy		
n	68	75
Mean ± SD	3 ± 2·5	4 ± 2·0
Range	0–15	0–8
Malignancy staging* (%)		
IA	4	5
IB	0	1
IIA	33	34
IIB	4	0
IIIA	46	54
IIIB	12	5
Haemoglobin (g/dl)		
Mean ± SD	9·3 ± 1·27	9·6 ± 0·95
Median	9·6	9·7
Range	5·7–11·5	7·4–11·8
Serum erythropoietin level (mU/ml)		
n	36	36
Median	116	93
Range	18–5220	10–408
Receiving transfusions (%)		
Yes	36	37
Haemoglobin (g/dl) at transfusion†		
n	25	28
Mean ± SD	8·1 ± 1·08	8·1 ± 0·93
Performance score (0–4)‡		
Missing	1	0
0	9	8
1	51	50
2	33	34
3	6	8

*Durie & Salmon (1975).
†For patients receiving transfusions at baseline.
‡The higher the score, the worse the patient's performance status.

Table II. Patients transfused during months 2 and 3 of the double-blind study.

	Epoetin alfa ($n = 69$)	Placebo ($n = 76$)	P-value
Transfused *n* (%)	19 (27·5)	36 (47·4)	0·017

Transfused (by transfusion history*) *n* (%)	Transfused prestudy	Not transfused prestudy	Transfused prestudy	Not transfused prestudy	*P*-value
	14 (56·0)	5 (11·4)	22 (78·6)	14 (29·2)	0·006

*Categorized as either having or not having received one or more transfusions during the prior 3 months.

patients randomized to receive epoetin alfa and 39/72 (54·2%) of patients randomized to receive placebo.

Sixty-four of 69 (92·8%) epoetin alfa patients and 61/76 (80·3%) placebo patients completed the 12 weeks of double-blind treatment. Five patients who received epoetin alfa discontinued prematurely, two because of adverse events (death due to septic shock, $n = 1$; disease progression, $n = 1$), and three for personal reasons. Fifteen patients who received placebo discontinued prematurely, three because of adverse events (pneumonia, $n = 1$; death due to septic shock, $n = 1$; death due to acute renal failure, $n = 1$); six because of disease progression; and six for personal ($n = 3$) or other unspecified reasons ($n = 3$).

The open-label phase of the study comprised 42/69 patients (60·9%) who initially received epoetin alfa and 45/76 patients (59·2%) who initially received placebo and was completed by 37/42 patients (88·1%) and 38/45 patients (84·4%) respectively. Adverse events (two patients per group) and disease progression (two patients per group) were the most frequently cited reasons for discontinuing the open-label phase of the study.

Transfusion requirements

As shown in Table II, significantly ($P = 0·017$) fewer patients required transfusions during months 2 and 3 of the study if they received epoetin alfa (19/69; 27·5%) compared with placebo (36/76; 47·4%). The effect favouring epoetin alfa was consistent when patients were stratified by transfusion history, i.e. significantly ($P = 0·006$) fewer patients who received epoetin alfa required blood transfusions during months 2 and 3 compared with patients who received placebo (Table II). Mean Hb levels during the double-blind phase that triggered transfusion were similar between the treatment groups, i.e. 7·66 g/dl (range, 6·1–9·7 g/dl) for epoetin alfa-treated patients and 7·89 g/dl (range, 6·47–9·45 g/dl) for placebo-treated patients.

Haematopoietic response

Haematopoietic response was evaluated for 132 patients who had completed at least 56 d of treatment (EFF population). In the double-blind phase of the study, patients who received epoetin alfa ($n = 66$) had an increase in mean Hb (± SD) of 1·8 ± 2·05 g/dl from baseline to last value, whereas patients who received placebo ($n = 66$) had no change in mean Hb over this period (0·0 ± 1·18 g/dl) (Fig 1). This difference between treatments in haematopoietic response was significant ($P < 0·001$). Mean Hb levels at baseline and week 12 were 9·2 and 11·2 g/dl, respectively, for patients who received epoetin alfa and 9·6 and 9·7 g/dl, respectively, for those who received placebo. When patients who had received placebo were administered epoetin alfa in the open-label phase ($n = 45$), mean Hb increased 2·4 g/dl; increases in mean Hb for patients who had been receiving epoetin alfa ($n = 42$) were maintained (Fig 2).

During the double-blind phase, haematopoietic response to epoetin alfa therapy was also evaluated in terms of *responders* (patients with Hb increases ≥ 2 g/dl unrelated to transfusion) and *correctors* (patients who achieved Hb levels ≥ 12 g/dl unrelated to transfusion). There were significantly ($P < 0·001$) more responders and correctors in the epoetin alfa group (38/66, 57·6% and 30/66, 45·5% respectively) than in the placebo group (6/66, 9·1% and 2/66, 3·0% respectively). The mean time required for responders in the epoetin alfa group ($n = 38$) to achieve an Hb level at least 2 g/dl above the baseline level was 46 d,

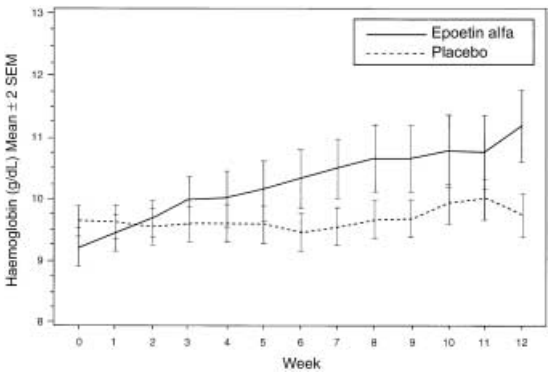

Fig 1. Mean weekly Hb levels for the efficacy population during the double-blind phase (weeks 0–12). Any values related to transfusion have been included, and missing values are replaced by the last observation carried forward.

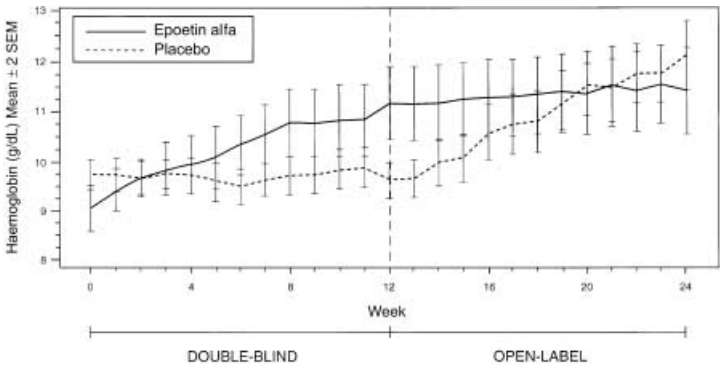

Fig 2. Mean weekly Hb levels for the double-blind and open-label phases (weeks 0–24) for the open-label population. Any values related to transfusion have been included, and missing values are replaced by the last observation carried forward. ('Placebo' refers to treatment during the double-blind phase; thereafter, patients in the placebo group who continued on study received epoetin alfa.)

and the mean time required for correctors in this group ($n = 30$) to achieve an Hb level ≥ 12 g/dl was 50 d. The mean times to response or correction in the placebo group were 35 d and 23 d respectively. However, although these changes appear to have occurred faster in the placebo group, the findings are most probably artefacts due to the very small numbers of placebo-treated responders ($n = 6$) and correctors ($n = 2$).

QOL assessment

Quality of life in the double-blind phase was evaluated for 138 (66 epoetin alfa and 72 placebo) patients with baseline and subsequent assessments. Both treatment groups showed some improvement in QOL. However, multivariate analysis did not discern a significant difference between the treatment groups for week-12 QOL change scores, although nearly all trends favoured patients treated with epoetin alfa. Univariate analyses of within-group mean changes from baseline to week 12 indicated significant improvement in four QOL scales for the epoetin alfa group and only one QOL scale for the placebo group. In the epoetin alfa group, significant improvement was noted in the NHP scales for emotional reactions ($P < 0{\cdot}001$) and social isolation ($P = 0{\cdot}05$) and for the CLAS items energy level ($P = 0{\cdot}01$) and ability to do daily activities ($P < 0{\cdot}001$); moreover, there was a trend towards significance for the CLAS item overall QOL ($P = 0{\cdot}07$). In the placebo group, only the NHP scale sleep showed significant ($P = 0{\cdot}03$) improvement between baseline and week 12, and the CLAS item overall QOL was virtually unchanged from baseline ($P = 0{\cdot}86$).

Quality of life in the open-label phase was evaluated for 78 patients who had clinical assessments through week 12, with QOL scores from week 4, 8 or 12 of the double-blind phase (whichever was the most recent) and subsequent assessments. Changes in QOL in patients who started or continued epoetin alfa treatment in the open-label phase of the study were evaluated using repeated-measures models. Only within-group analyses were performed, as the two cohorts may not have been comparable at the beginning of the open-label treatment. A consistent trend towards improved QOL in three out of six NHP scales (energy, sleep, physical mobility) and all three CLAS items (energy level, ability to do daily activities, overall QOL) was observed for patients in the placebo-to-epoetin alfa cohort at week 24, i.e. the end of the open-label phase. In the group that continued on epoetin alfa, the improvement in QOL observed during the double-blind phase was generally maintained during the open-label phase.

Performance and global assessments

The overall change from baseline in performance scores during the double-blind study phase significantly ($P = 0{\cdot}038$) favoured the epoetin alfa group over the placebo group. A one-point improvement in performance score, i.e. the ability to perform tasks of daily living, was noted in 19·7% (13/66) of patients who received epoetin alfa and 6·1% (4/66) of patients who received placebo. A two-point deterioration in physical ability was recorded for 1·5% (1/66) of patients who received epoetin alfa and 7·6% (5/66) of patients who received placebo. Changes in performance scores during the open-label phase of the study were calculated from the end of double-blind treatment to termination. During the open-label phase, 20·0% (9/45) of patients who had received placebo during the double-blind phase had a one-point improvement in performance score, and 2·2% (1/45) had a two-point improvement. Performance score improved one point in 9·5% (4/42) of patients who continued to receive epoetin alfa; however, no patient who continued on epoetin alfa had two-point or greater improvement. No change in score was noted for 59·5% of patients who continued to receive epoetin alfa and 53·3% of patients who had previously received placebo. A worsening in performance score was noted for 23·8% (10/42) of patients who continued to receive epoetin alfa and 20·0% (9/45) of patients who had previously received placebo.

Response to study treatment for anaemia was rated globally by the physician as excellent, very good, good, fair or poor. Comparative responses for the epoetin alfa and placebo patients, respectively, were: excellent, 19·7% vs. 0·0%; very good, 19·7% vs. 3·0%; good, 13·6% vs. 9·1%; fair, 18·2% vs. 24·2%; and poor, 28·8% vs. 63·6%. The difference in poor response was significant ($P < 0{\cdot}001$).

Safety assessments

Table III shows the incidence of adverse events reported in 10% or more of patients in any treatment group during the

Table III. Incidence of adverse events in ≥ 10% of patients in any treatment group during double-blind and open-label treatment.

Adverse event	Double-blind treatment* EPO ($n = 69$) n (%)	Double-blind treatment* PBO ($n = 76$) n (%)	Open-label treatment EPO + EPO† ($n = 42$) n (%)	Open-label treatment PBO + EPO† ($n = 45$) n (%)
Any adverse event	50 (72·5)	57 (75·0)	24 (57·1)	30 (66·7)
Fever	5 (7·2)	10 (13·2)	5 (11·9)	3 (6·7)
Pain	9 (13·0)	3 (3·9)	4 (9·5)	3 (6·7)
Skeletal pain	5 (7·2)	2 (2·6)	5 (11·9)	2 (4·4)
Leucopenia	9 (13·0)	6 (7·9)	3 (7·1)	2 (4·4)
Granulocytopenia	3 (4·3)	4 (5·3)	4 (9·5)	1 (2·2)
Dyspnoea	2 (2·9)	3 (3·9)	4 (9·5)	1 (2·2)
Hypertension	3 (4·3)	1 (1·3)	4 (9·5)	1 (2·2)
Infection	1 (1·4)	4 (5·3)	1 (2·4)	5 (11·1)

EPO, epoetin alfa; PBO, placebo.
*Weeks 0–12.
†Weeks 12–24. First-mentioned drug was administered during the double-blind treatment phase; all patients who entered the open-label phase received epoetin alfa.

double-blind and open-label phases of the study. No differences were found for overall incidence of adverse events in the double-blind phase (72·5% epoetin alfa-treated; 75·0% placebo-treated) and the open-label phase (57·1% who continued epoetin alfa; 66·7% who had previously received placebo); type and frequency of individual adverse events were similar throughout the study. The most commonly reported adverse events in either treatment group were fever, pain and leucopenia.

Disease response to chemotherapy (i.e. responsive, improved, stable or unresponsive) was comparable between patients who received epoetin alfa and those who received placebo, i.e. treatment with epoetin alfa did not appear to influence the effects of cytotoxic treatment or disease status. Fourteen patients died during the study, eight during double-blind treatment (one epoetin alfa, seven placebo) and six during open-label treatment (two who continued epoetin alfa, four who had received placebo). No deaths were considered to be related to the study drug, and 50% of the deaths were attributed to disease progression. The remaining seven patients died of septic shock/infection (4), acute renal failure (2) or cardiogenic shock (1).

DISCUSSION

Patients with multiple myeloma, particularly those who are chemotherapy refractory or chemotherapy resistant, often require correction of disease- or chemotherapy-related anaemia. In the double-blind, placebo-controlled study reported here, administration of epoetin alfa, compared with placebo, significantly ($P = 0·017$) reduced transfusion requirements and increased Hb levels by ≥ 2 g/dl in significantly more patients than did placebo (57·6% vs. 9·1%, $P < 0·001$). The increase in Hb levels in the placebo group presumably was due at least in part to the higher transfusion rate in this group, possibly in combination with disease response to chemotherapy.

These results further support those of other clinical studies that have documented the efficacy of epoetin alfa in increasing Hb levels and reducing transfusion requirements in anaemic patients with non-myeloid malignancies, including multiple myeloma (Abels, 1993; Ludwig *et al*, 1993, 1995; Dunphy *et al*, 1997; Glaspy *et al*, 1997; Demetri *et al*, 1998). Several studies were conducted specifically in multiple myeloma patients who had received or were receiving chemotherapy for advanced or longstanding disease and had severe anaemia. In two of these studies, response to epoetin alfa, defined in those studies as an increase of 2 g/dl or more in Hb level, was noted in 85% (11/13) (Ludwig *et al*, 1990) and 71% (12/17) (Mittelman *et al*, 1997) of patients, and transfusion requirements were completely eliminated in at least 77% (≥ 10/13) and 55% (6/11) of patients respectively.

The haematological benefits of epoetin alfa were also observed in patients with progressive multiple myeloma who were considered resistant or refractory to chemotherapy. Patients in two controlled, comparative studies were randomized to either epoetin alfa treatment or no epoetin alfa treatment (control group) (Silvestris *et al*, 1995; Dammacco *et al*, 1998). Patients were also stratified by transfusion requirements. In one of the studies, a significantly ($P \leq 0·001$) greater percentage of patients who received epoetin alfa (75%), compared with control patients (21%), had increased Hb levels and/or reduced transfusion requirements, regardless of prestudy transfusion history (Dammacco *et al*, 1998). In the second study, 78% (21/27) of patients who received epoetin alfa had an increase in Hb of ≥ 2 g/dl; 55% (6/11) of evaluable patients transfused before study entry no longer required transfusions after 2 months of epoetin alfa treatment (Silvestris *et al*, 1995).

A small proportion of patients, i.e. those with smouldering multiple myeloma or non-responding, non-progressive myeloma, have asymptomatic disease and therefore should not receive chemotherapy (San Miguel *et al*, 1999).

However, these patients often develop anaemia serious enough to require intervention, and may be treated with chemotherapy because of the anaemia. In a report of a study that included three patients with smouldering multiple myeloma, use of epoetin alfa to ameliorate anaemia in these patients, who were asymptomatic and had never received chemotherapy, allowed postponement of chemotherapy for 6 months in one patient and, as of the report date, 42 months in another patient (Garton *et al*, 1995). Thus, the use of epoetin alfa may obviate, at least temporarily, the need for some patients to start chemotherapy.

Changes in functional status and QOL in the study reported here were secondary efficacy assessments, and the study was not powered to measure absolute change, but rather statistical trends. Despite this limitation, analysis of within-group changes from baseline to week 12 revealed significant ($P = 0{\cdot}05$ to $P < 0{\cdot}001$) improvement in emotional reactions, social interaction, energy and ability to do daily activities in patients treated with epoetin alfa. Placebo-treated patients, in contrast, showed no significant improvement except in sleep. Between-group differences in effect on QOL were not detected. However, the overall change in performance scores, which was indicative of improvement, was significantly greater for patients who received epoetin alfa compared with placebo. Coupled with this finding was a two-point deterioration in performance score for more patients who received placebo compared with those who received epoetin alfa. In all, nearly 20% of epoetin alfa-treated patients experienced improved performance during the double-blind phase, compared with 6% of placebo-treated patients. These findings are consistent with those of several earlier studies that reported enhancement of functional capacity and QOL when cancer patients, including those with multiple myeloma, were treated with epoetin alfa to alleviate their anaemia (Ludwig *et al*, 1990; Abels, 1992; Leitgeb *et al*, 1994; Glaspy *et al*, 1997; Mittelman *et al*, 1997; Demetri *et al*, 1998). These studies generally had large patient populations (Abels, 1992; Glaspy *et al*, 1997; Demetri *et al*, 1998) or specifically evaluated QOL (Leitgeb *et al*, 1994) and used a variety of validated instruments to measure changes in functional capacity and QOL. In three of the studies, epoetin alfa therapy resulted in significant ($P < 0{\cdot}05$ to $P < 0{\cdot}001$) improvement in several measures of QOL including energy, activity, feeling of well-being and overall QOL (Leitgeb *et al*, 1994; Glaspy *et al*, 1997; Demetri *et al*, 1998). Another study in this series, a small ($n = 13$), open-label trial conducted in multiple myeloma patients only, reported QOL changes as a heightened sense of well-being and increase in exercise tolerance, which were reflected by significant ($P < 0{\cdot}02$) changes in performance scores (Ludwig *et al*, 1990).

When placebo patients were given epoetin alfa in the open-label phase of the study reported here, trends towards improvement were noted in most QOL variables, although no statistically significant changes were discerned in any parameter. That no significant changes in QOL were reported in these 45 patients is not surprising, given the relatively small patient number on which this analysis was based. However, as in the double-blind phase of the study, administration of epoetin alfa during the open-label phase resulted in improvement in performance scores, with about 22% of patients experiencing increased performance – a rate comparable to that noted in patients who received epoetin alfa for the 12 weeks of double-blind treatment. Also, during the open-label phase, performance scores remained stable for more than half the patients who continued to receive epoetin alfa (59·5%), as well as for those who had previously received placebo (53·3%), while worsening in 23·8% and 20·0% of patients in the respective treatment groups. These findings suggest that epoetin alfa may be useful in both improving and maintaining QOL in multiple myeloma patients.

This study did not address the length of time epoetin alfa should be continued before a decision is made to discontinue treatment because of the improbability of the patient achieving a therapeutic response. However, the maximum times to response were 88 d for an Hb increase of ≥ 2 g/dl and 83 d for an Hb increase of ≥ 12 g/dl. These times were similar to the maximum of 84 d for an Hb level increase of ≥ 2 g/dl, haemoglobin level of ≥ 12 g/dl or both, reported in a large, community-based study that included nearly 2300 evaluable patients (Demetri *et al*, 1998). In the small study mentioned earlier, the maximum time to response was approximately 140 d (Ludwig *et al*, 1990). Based on these data, an estimated trial of epoetin alfa for 3–4 months would seem reasonable.

Epoetin alpha was well tolerated; adverse events were similar between the active drug and placebo groups during double-blind treatment and remained relatively constant and comparable during open-label treatment.

In conclusion, the results of this study provide further evidence that epoetin alfa is an effective and well-tolerated agent for the management of myeloma-associated anaemia. Benefits include prevention or amelioration of anaemia, reduction in transfusion requirements and improvement in QOL.

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