Eur J Cancer, Vol. 29A, Suppl. 2, pp. S2-S8, 1993
Printed in Great Britain

0964-1947/93 $6.00+0.00

Erythropoietin for Anaemia in Cancer Patients

R. Abels

INTRODUCTION

ADVANCED CANCER is frequently associated with significant anaemia which may be worsened by the administration of chemotherapy with myelotoxic agents such as methotrexate or nephrotoxic agents such as cisplatin. Although anaemia in cancer patients may be multifactorial in origin, it is often categorised as the anaemia of chronic disease (ACD) [1,2]. ACD is characterised by erythroid hypoplasia of the bone marrow, a modest decrease in red cell survival, decreased bone marrow reutilization of iron, and inappropriately low erythropoietin levels for the degree of anaemia [2]. Consistent with this ACD model, inappropriately low serum erythropoietin levels for the degree of anaemia have recently been documented in cancer patients [3].

The symptomatology of anaemia may contribute substantially to the overall lack of well-being that cancer patients frequently experience during their disease process. The transfusions often required for palliation of these symptoms carry significant risks. There is an estimated 20% probability of some associated adverse effect including fever, chills, rash, urticaria and exposure to hepatitis [4]. The scope of this problem is substantial when one considers that the annual transfusion estimate for this patient group in the U.S.A. alone is one million units of red blood cells/whole blood [5].

The observation that, at any given haemoglobin level, serum erythropoietin levels tend to be lower in cancer patients than in iron deficiency patients [3] suggests that anaemia in cancer is at least partially due to a relative deficiency of erythropoietin. In conjunction with this observation, recent work demonstrating both the efficacy and safety of recombinant human erythropoietin (r-HuEPO) in increasing haematocrit in anaemic patients with chronic renal failure [6,7] and in anaemic, zidovudine (AZT)-treated HIV-infected patients [8] offers the possibility that exogenous erythropoietin may also be an effective treatment for anaemia in cancer patients.

To test this possibility, we conducted a series of double-blind, placebo-controlled trials using r-HuEPO in anaemic cancer patients in three different patient populations to examine the safety of r-HuEPO treatment, and its impact on haematocrit, transfusion requirements and quality of life. The three populations were: patients receiving no chemotherapy, patients receiving cyclic non-cisplatin-containing chemotherapy and patients receiving cyclic cisplatin-containing chemotherapy.

PATIENTS AND METHODS

A total of 413 patients were enrolled in this program. The number of patients in each study type was as follows: no chemotherapy (NC, n=124), cyclic non-cisplatin-containing chemotherapy (NCC, n=157) and cyclic cisplatin-containing chemotherapy (CC, n=132). For entry into the study, patients had to be ≥18 years of age with a biopsy-proven diagnosis of cancer (with primary myeloid malignancies and acute leukaemias excluded). Anaemia was defined as a haematocrit of ≤32% (or a haemoglobin ≤10.5 g/l). All patients had a performance status ≤3 on the ECOG scale, were clinically stable for at least 1 month prior to study entry, and had an anticipated life expectancy of ≥3 months. For the two types of chemotherapy trials, cyclic chemotherapy was to be administered ≤5 days every 3–4 weeks.

Exclusion criteria other than type of cancer were: known cerebral metastases, uncontrolled hypertension, acute illness within 7 days of study entry, radiation or surgery within 30 days of study entry, experimental therapy within 30 days of study entry, androgen therapy within 2 months of study entry, evidence of renal insufficiency (i.e. serum creatinine ≥2 mg/dl), evidence of folate, B_{12} and/or iron deficiency, autoimmune haemolysis or presence of gastrointestinal bleeding.

After giving informed consent, patients in each trial category were randomised to experimental and control groups. NC patients were randomised to r-HuEPO 100 U/kg or placebo given subcutaneously (SC) three times/week for up to 8 weeks. NCC and CC patients were randomised to r-HuEPO 150 U/kg or placebo SC three times/week for 12 weeks. After completion of double-blind therapy, patients were eligible to receive r-HuEPO on an open-label basis, but this report describes the double-blind phase only. The r-HuEPO used in these trials was produced by Chinese hamster ovary cells transfected with the human erythropoietin gene, and was manufactured by Amgen, Inc. of Ortho Biologics, Inc.

The major efficacy criteria were the effects of treatment on haematocrit and transfusion requirements. Haematocrit analyses included comparison of the change from baseline to final value in the r-HuEPO and placebo groups, comparison of mean weekly haematocrit in the r-HuEPO and placebo groups, and comparison in each group of *"correctors"* (patients who attained a haematocrit ≥38% unrelated to transfusion) and *"responders"* (patients whose haematocrit increased ≥6% unrelated to transfusion). *"Unrelated to transfusion"* means that no transfusion was administered in the month prior to documenting attainment of the criterion. Transfusion analyses included comparison of the mean number of units of blood transfused per patient and the proportion of patients transfused in each experimental and control group.

Two additional variables were inspected to assess homogeneity between experimental and control groups in relation to improvement of anaemia associated with r-HuEPO therapy. The transfusion trigger was determined in both r-HuEPO- and placebo-treated patients to ensure that results were not influenced by differential transfusion practice. In the chemotherapy trials, the intensity of chemotherapy was measured to be sure that results did not reflect less intense chemotherapy in the r-HuEPO-treated

Correspondence to R. Abels at the R. W. Johnson Pharmaceutical Research Institute, Raritan, New Jersey, U.S.A.
Revised 1 Mar. 1993; accepted 17 Mar. 1993.

group. Since the patients in the two types of chemotherapy trials received a wide variety of different chemotherapy regimens, it was thought best to use a surrogate marker for the intensity of chemotherapy. The most appropriate surrogate markers for intensity of chemotherapy, particularly for the intensity of chemotherapy-induced myelosuppression, appeared to be the effect of chemotherapy on neutrophil and platelet counts. Neutrophil analyses included area under the neutrophil time curve, and percentage of patients with neutrophils <1000 or <500 cells/μl. The platelet analyses included change in platelet count from baseline to final values, and the percentage of patients whose platelet count fell to <50 000 or <20 000 per μl. In addition, within the CC group we compared cisplatin dosage between r-HuEPO- and placebo-treated patients. Other analyses included the determination of whether tumour type (haematological vs. non-haematological) or tumour infiltration of the bone marrow influenced the response to therapy.

Lastly, we assessed the impact of r-HuEPO therapy on quality-of-life parameters. Both before and after the study period, patients responded to a questionnaire composed of Visual Analogue Scales designed to assess their preceding week with respect to energy level, ability to perform daily activities and overall quality of life. Each question was answered by placing a vertical mark on a 100 mm line representing a continuum from the lowest to the highest assessment for that item.

Patients were considered evaluable for efficacy if they completed ≥15 days on study; all patients were evaluable for safety. Fischer's exact test was used for statistical inference for dichotomous variables (e.g. sex by treatment group) formulated as 2x2 tables. The extended Mantel–Haenszel test with integer scores was used for other types of discrete data. Between-group comparisons of means were analysed with two-sample *t*-tests, and changes from baseline to final value were analysed via paired *t*-tests. A linear model approach was used for inference on major efficacy variables such as transfusion requirements. These models were constructed with treatment group and covariant factors such as endogenous serum EPO level, haematocrit, performance score, etc. All statistical tests of hypotheses were two-sided, with $\alpha = 0.05$.

RESULTS

Demographic and baseline characteristics

Of the total number of patients enrolled, 213 were randomised to r-HuEPO and 200 were randomised to placebo. Of these two groups, 206 r-HuEPO-treated patients and 190 placebo-treated patients were evaluable for efficacy. Pooling patients across all trials shows equivalent demographic characteristics between the patients randomised to r-HuEPO and the patients randomised to placebo (Table 1). The average patient was a 62-year-old Caucasian with an essentially equal probability of being male or female. The mean weight of about 67 kg would suggest that these patients were not grossly wasted at baseline. One-third of the patients in each treatment group had haematological tumours. Although the non-haematological tumours were widely distributed in terms of the organ affected, this distribution was quite similar in the r-HuEPO and placebo groups. Approximately 46.5% of the patients were transfused during the pretreatment baseline period (2 months for the NC trials, 3 months for the NCC and CC trials), with approximately 0.70 units of blood transfused per patient during each baseline month. The mean baseline haematocrit, between 28–29%, was obviously somewhat elevated by the effect of prior red cell transfusions. Neutrophil counts were adequate. Overall pretreatment quality of life was about 50 mm on the scale of 0–100 mm, indicating significant functional impairment at baseline.

The distribution of baseline endogenous serum erythropoietin levels is shown in Fig. 1. The median level was lowest in the cisplatin chemotherapy group (see Table 2), which is perhaps related to this agent's nephrotoxic effect. The overall frequency distribution shows the mode occurring at the lowest end, in the 0–50 mU/ml range, with about 75% of the patients having baseline values below 150 mU/ml, and fewer than 5% above 500 mU/ml (see Fig. 1).

Table 1. Demographic and baseline characteristics

Parameter	r-HuEPO*	Placebo*
Sex		
Male	102	95
Female	111	105
Race		
White	179	172
Other	34	28
Age (years)	61.2±13.0	62.5±12.3
Weight (kg)	67.8±14.0	67.0±14.1
Height (inches)	66.5±4.2	66.2±4.1
Percentage transfused	44.7	48.4
Units transfused/patient/month	0.67±1.08	0.73±1.04
Mean haematocrit (%)	29.1±4.0	28.5±3.8
Neutrophil count (cells/μl)	4163±3386	4017±3424
Endogenous serum EPO level (mU/ml)		
Mean	146±260	149±217
Median	76	85
Overall quality of life (mm on 100-mm scale)	50.0±24.0	50.4±26.0
Tumour type (%)		
Haematological	32.0	32.1
Non-haematological	68.0	67.9
Prostate	11.2	9.0
Breast	10.7	12.6
Gastrointestinal	10.2	5.3
Lung, non-small cell	10.2	9.0
Gynaecological	9.2	12.1
Lung, small cell	3.9	8.0
Head and neck	2.4	1.6
Oesophagus	1.0	1.6
Unknown primary site	3.4	1.1
Others	5.8	7.9

*Data for demographic characteristics (i.e. sex, race, age, weight, height) were averaged over the entire enrolled patient population, so that the r-HuEPO-treated group n=213, and the placebo-treated group n=200. Data for other baseline characteristics represent all patients evaluable for efficacy, so that the r-HuEPO-treated group n=206 and the placebo-treated group n=190. (Reproduced by permission from *Acta Haematologica* 1992, **87**, Suppl. 1, 4–11.)

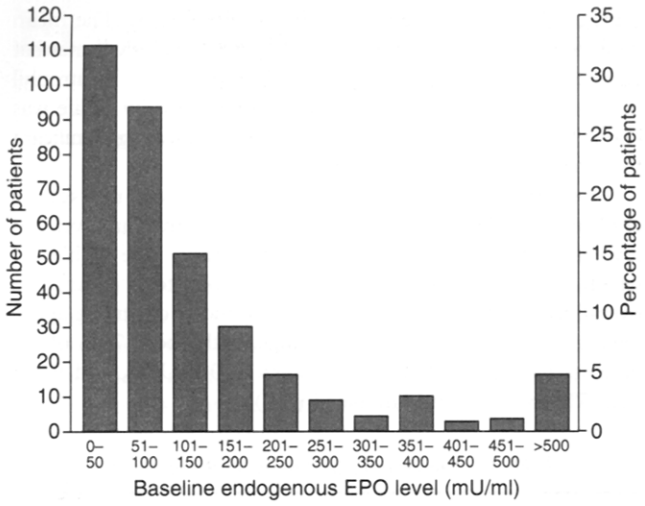

Fig. 1. Baseline endogenous erythropoietin level (all studies combined; n=348). (Reproduced by permission from *Blood Cell Growth Factors: Their Present and Future Use in Hematology and Oncology. Proceedings of the Beijing Symposium.* Martin J. Murphy, Jr., ed. Dayton, Ohio: AlphaMed Press, 1991.)

Haematocrit

In each of the three cancer trial groups, mean weekly haematocrit remained stable among placebo-treated patients but increased progressively in the r-HuEPO-treated group over the 8–12-week course of therapy (Fig. 2). The improvement from baseline to final value (Table 3) was significantly greater for all three r-HuEPO treatment groups compared to the corresponding changes in placebo-treated patients (P <0.004). In addition, all three r-HuEPO-treated groups contained a significantly (P <0.008) greater percentage of both correctors (achieving the 38% haematocrit target) and responders (haematocrit increase ≥6%) compared to placebo (Table 4). The differences were most striking within the two chemotherapy trial groups. The smaller increase in haematocrit parameters in the NC group may have been related to the lower dose (100 U/kg three times/week) and shorter treatment time (8 weeks) compared to the CC and NCC groups (150 U/kg three times/week for 12 weeks).

Transfusion requirements

Compared to placebo, the three r-HuEPO-treated groups consistently had a smaller mean proportion of patients transfused and less blood transfused per patient over the entire course of observation, although these differences were not statistically significant (Table 5). On the assumption that r-HuEPO would be most likely to reduce transfusion requirements during the latter portion of therapy, and would be least likely to affect transfusion requirements during the early portion of therapy, transfusion data were stratified by period of therapy, i.e. month 1 vs. months 2 and 3 combined (Table 6). Looking at each chemotherapy study separately, transfusion requirements were similar in r-HuEPO- and placebo-treated patients during the first month of therapy. During the final 2 months of therapy, however, transfusion requirements were substantially lower in the r-HuEPO-treated patients compared to the placebo-treated group. When data from the two chemotherapy groups were combined, r-HuEPO- and placebo-treated patients had equivalent transfusion requirements

Table 2. Median baseline serum erythropoietin levels and haematocrits

	Serum EPO (mU/ml)	Haematocrit (%)
No chemotherapy	89.5	29.0
Chemotherapy	94.5	29.0
Cisplatin chemotherapy	54.0*	29.0

*Significantly (P<0.05) less than chemotherapy and no chemotherapy values. (Reproduced by permission from *Blood Cell Growth Factors: Their Present and Future Use in Hematology and Oncology. Proceedings of the Beijing Symposium.* Martin J. Murphy, Jr., ed. Dayton, Ohio: AlphaMed Press, 1991.)

Table 3. Change in haematocrit from baseline to last value

Treatment	n	Baseline value (%)	Final value (%)	Percentage point change
No Chemotherapy				
r-HuEPO	63	29.3±4.0	32.1±6.8	2.8±6.3*
Placebo	55	27.6±3.9	27.5±4.0	-0.1±4.0
Chemotharepy				
r-HuEPO	79	28.6±3.9	35.5±6.0	6.9±6.0*
Placebo	74	29.4±3.0	30.5±4.0	1.1±4.3
Cisplatin				
r-HuEPO	64	29.4±4.0	35.4±7.0	6.0±7.0*
Placebo	61	28.4±14.5	29.7±4.5	1.3±5.0

*Significantly (P<0.004) greater than placebo. (Reproduced by permission from *Blood Cell Growth Factors: Their Present and Future Use in Hematology and Oncology. Proceedings of the Beijing Symposium.* Martin J. Murphy, Jr., ed. Dayton, Ohio: AlphaMed Press, 1991. *Acta Haematologica* 1992, **87**, Suppl. 1, 4-11.)

Table 4. Correction of anaemia: response to therapy unrelated to transfusion

Study type/ treatment group	n	Percentage of patients Correctors (HCT>38%)	Responders (HCT ≥6%)
No Chemotherapy			
r-HuEPO	63	20.6*	31.7*
Placebo	55	3.6	10.9
Chemotherapy			
r-HuEPO	79	40.5*	58.2*
Placebo	74	4.1	13.5
Cisplatin			
r-HuEPO	64	35.9*	48.4*
Placebo	61	1.6	6.6

*Significantly (P<0.008) greater than placebo. (Reproduced by permission from *Blood Cell Growth Factors: Their Present and Future Use in Hematology and Oncology. Proceedings of the Beijing Symposium.* Martin J. Murphy, Jr., ed. Dayton, Ohio: AlphaMed Press, 1991. *Acta Haematologica* 1992, **87**, Suppl. 1, 4-11.)

during the first month of therapy, but the r-HuEPO group had significantly lower transfusion requirements than the placebo-treated group did for the combined second and third months (see Table 6). On the other hand, there was no reduction in transfusion requirements after month 1 of therapy in the r-HuEPO-treated patients compared to the placebo-treated group in the NC trial, perhaps related to the relatively low dose of r-HuEPO administered and short duration of follow-up in this trial.

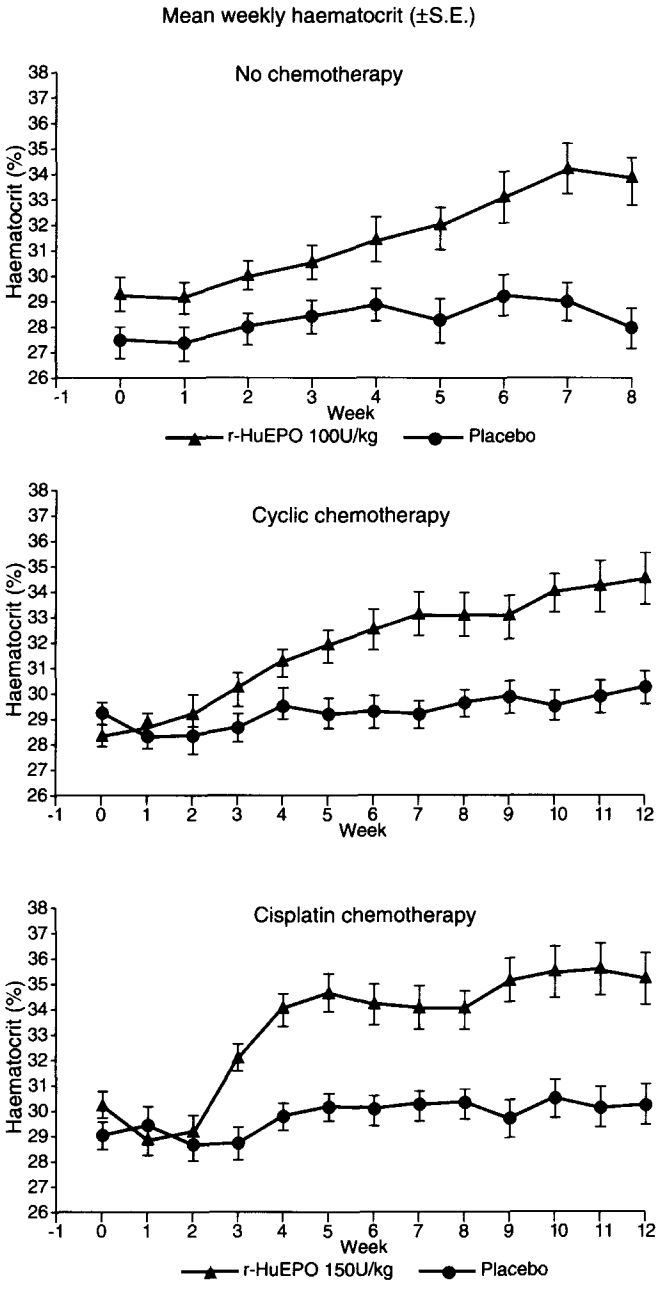

Fig. 2. Mean weekly haematocrit (±S.E.) comparing r-HuEPO treatment and placebo for each treatment group. (Reproduced by permission from *Blood Cell Growth Factors: Their Present and Future Use in Hematology and Oncology. Proceedings of the Beijing Symposium.* Martin J. Murphy, Jr., ed. Dayton, Ohio: AlphaMed Press, 1991. *Acta Haematologica* 1992, 87, Suppl. 1, 4-11.)

Table 5. Average transfusion requirements in r-HuEPO- and placebo-treated patients

Study type/ treatment group	*n*	Proportion of patients transfused (%)	Mean units of blood transfused per patient*
No chemotherapy			
r-HuEPO	63	33.3	1.52±2.61
Placebo	55	38.2	2.19±3.57
Chemotherapy			
r-HuEPO	79	40.5	2.03±3.88
Placebo	74	48.6	2.75±4.15
Cisplatin			
r-HuEPO	64	53.1	3.56±7.01
Placebo	61	68.9	4.01±4.87

*Gross mean units transfused/patient. (Reproduced by permission from *Blood Cell Growth Factors: Their Present and Future Use in Hematology and Oncology. Proceedings of the Beijing Symposium.* Martin J. Murphy, Jr., ed. Dayton, Ohio: AlphaMed Press, 1991.)

Table 6. Transfusion requirements in chemotherapy patients by month

Chemotherapy group	Month 1 *n*	Month 1 (%) Trans-fused	Month 1 Units/ Patient*	Months 2–3 *n*	Months 2–3 (%) Trans-fused	Months 2–3 Units/ Patient*
Non-cisplatin						
r-HuEPO	79	25.3	0.69	70	28.6	0.91
Placebo	74	27.0	0.71	68	36.8	1.65†
Cisplatin						
r-HuEPO	64	43.8	1.71	56	26.8	1.20
Placebo	61	44.3	1.20	55	56.4§	2.02*
Total						
r-HuEPO	143	33.6	1.09	126	27.8	1.04
Placebo	135	34.8	0.98	123	45.5§	1.81‡

*Adjusted by linear model for baseline factors such as endogenous serum EPO level. *P=0.089; †P=0.056; ‡P=0.009; §$P \leq 0.005$. (Reproduced by permission from *Blood Cell Growth Factors: Their Present and Future Use in Hematology and Oncology. Proceedings of the Beijing Symposium.* Martin J. Murphy, Jr., ed. Dayton, Ohio: AlphaMed Press, 1991. *Acta Haematologica* 1992, 87, Suppl. 1, 4-11.)

Table 7. Mean haematocrit at time of transfusion

Study type	Mean haematocrit (%) and range (%) at time of transfusion r-HuEPO	Placebo
No chemotherapy	24.7 (20.9–32.3)	24.2 (20.2–29.0)
Chemotherapy	24.5 (20.1–33.0)	24.8 (21.2–30.1)
Cisplatin chemotherapy	24.7 (20.7–29.9)	25.4 (19.0–30.1)

(Reproduced by permission from *Blood Cell Growth Factors: Their Present and Future Use in Hematology and Oncology. Proceedings of the Beijing Symposium.* Martin J. Murphy, Jr., ed. Dayton, Ohio: AlphaMed Press, 1991.)

*Table 8. Intensity of chemotherapy**

Parameter	Chemotherapy r-HuEPO (n=79)	Chemotherapy Placebo (n=74)	Cisplatin chemotherapy r-HuEPO (n=64)	Cisplatin chemotherapy Placebo (n=61)
AUC (cells x week/μl)†	30203	34189	33289	33453
% Patients with ANC <1000 cells/μl	64.6	64.9	82.8	77.0
% Patients with ANC <500 cells/μl	40.5	31.1	59.4	49.2
Change in platelets from baseline to final value x 10^3	-39.0	-48.0	-101.2	-97.3
% Patients with platelets <50000/μl	22.8	23.0	35.9	34.4
% Patients with platelets <20000/μl	2.5	2.7	10.9	6.6
Total cisplatin dose (mg)	—	—	272.9	294.4

*Patients evaluable for efficacy in the non-cisplatin-containing and cisplatin-containing chemotherapy groups. †Area under the neutrophil time curve. No statistically significant ($P>0.05$) differences between r-HuEPO response and corresponding placebo response. (Reproduced by permission from *Blood Cell Growth Factors: Their Present and Future Use in Hematology and Oncology. Proceedings of the Beijing Symposium.* Martin J. Murphy, Jr., ed. Dayton, Ohio: AlphaMed Press, 1991. *Acta Haematologica* 1992, **87**, Suppl. 1, 4-11.)

Data on both transfusion trigger and chemotherapy intensity were collected to determine whether or not these factors affected the improvement observed in r-HuEPO-treated patients. In terms of transfusion trigger (Table 7), the haematocrit at which transfusion was administered was the same for r-HuEPO and placebo patients in all three trial groups. Chemotherapy intensity for r-HuEPO and placebo patients (Table 8) was not significantly different ($P>0.05$) based on comparison of neutrophil and platelet parameters in both trial groups. The total doses of cisplatin administered to r-HuEPO- and placebo-treated CC patients were also equivalent. Consequently, these factors did not appear to affect the response to r-HuEPO therapy.

Response and tumour type/infiltration of the bone marrow

Data for change in haematocrit from baseline to final value in various tumour types was pooled across all trial groups (Table 9). In eight types of cancer, r-HuEPO patient groups consistently increased their haematocrit more than placebo-treated patients did. The difference was significant in five tumour types ($P<0.05$), and approached significance in two others. The smallest increase among r-HuEPO-treated patients was found in those with prostate cancer due to the fact, perhaps, that most of these patients were treated in the non-chemotherapy trial with an r-HuEPO dose of only 100 U/kg three times per week for only 8 weeks.

At baseline, 32% of the r-HuEPO-treated patients had haematological tumours, and 68% had solid tumours (Table 10). Thirty-four per cent of the r-HuEPO-treated responders (i.e. haematocrit increased ≥6%) had haematological tumours and 66% had solid tumours. The equivalent distribution of haematological and solid tumours in the r-HuEPO-treated group as a whole and in the r-HuEPO-treated responder population suggests that both types of tumour respond equivalently to r-HuEPO therapy. Tumour infiltration of the bone marrow was present in 28% of the r-HuEPO-treated population as a whole, based on review of available clinical data (Table 10). Twenty-six per cent of the r-HuEPO-treated responders had baseline evidence of tumour infiltration of the bone marrow. The similar distribution of this parameter in the entire r-HuEPO-treated population and in the r-HuEPO-treated responder group suggests that patients with or without tumour infiltration of the bone marrow respond similarly to r-HuEPO therapy.

Quality of life

When the data were pooled across all of the cancer trial groups, the quality of life measures reflected a modest improvement in r-HuEPO-treated patients compared to

Table 9. Change in haematocrit from baseline to final value in various tumour types*

Tumour type	r-HuEPO n	r-HuEPO Baseline HCT (%)	r-HuEPO Change in HCT (%)	Placebo n	Placebo Baseline HCT (%)	Placebo Change in HCT (%)
CLL	7	29.5	6.0†	9	29.7	0.9
Myeloma	19	29.8	3.7‡	23	28.7	0.3
Lymphoma	40	29.5	6.0§	29	29.5	0.5
Breast cancer	22	28.4	6.5§	24	29.3	1.6
Lung cancer	29	29.2	6.4§	32	28.6	1.1
Prostate cancer	23	28.3	2.3	17	27.2	0.1
GI cancer	21	28.2	5.8§	10	28.3	1.6
Gynaecological cancer	18	28.2	7.7§	23	28.0	-0.3

*Since the data for any tumour type may include patients from the NC, NCC and CC treatment groups, duration of therapy can range from 8 (NC) to 12 (NCC, CC) weeks. †$P=0.077$ for difference between r-HuEPO and placebo. ‡$P=0.058$ for difference between r-HuEPO and placebo. §$P\leq0.05$ for difference between r-HuEPO and placebo. (Reproduced by permission from *Blood Cell Growth Factors: Their Present and Future Use in Hematology and Oncology. Proceedings of the Beijing Symposium.* Martin J. Murphy, Jr., ed. Dayton, Ohio: AlphaMed Press, 1991. *Acta Haematologica* 1992, **87**, Suppl. 1, 4-11.)

Table 10. Effect of tumour type and bone marrow infiltration on response to therapy

Parameter	Baseline distribution (%)	Among responders* (%)
Tumour type		
Haematological	32.0	34.0
Solid	68.0	66.0
Bone marrow infiltration†		
Yes	28.0	25.8
No	72.0	74.2

*97 r-HuEPO-treated patients increased HCT ≥6 percentage points unrelated to transfusion. †Based on review of available clinical data. (Reproduced by permission from *Blood Cell Growth Factors: Their Present and Future Use in Hematology and Oncology. Proceedings of the Beijing Symposium.* Martin J. Murphy, Jr., ed. Dayton, Ohio: AlphaMed Press, 1991. *Acta Haematologica* 1992, **87**, Suppl. 1, 4-11.)

placebo for each parameter, but attained significance only for overall quality of life ($P < 0.05$) (Fig. 3). When the comparison was restricted to r-HuEPO responders against all placebo-treated patients, however, a significant improvement in all three parameters that measured quality of life emerged in association with r-HuEPO therapy ($P < 0.05$) (Fig. 4).

Adverse experiences

Adverse experiences reported by at least 10% of patients in either treatment group were very similar (Table 11). The one exception was the greater frequency of shortness of breath ($P < 0.03$) occurring among placebo-treated patients. Five per cent of r-HuEPO-treated patients had hypertension reported as an adverse experience compared to 3.5% in the placebo-treated group. Although the difference was not significant, individual case histories suggest that r-HuEPO-treated patients may occasionally experience hypertension as a result of a significant increase in haematocrit. In addition, no antibodies against r-HuEPO developed during the course of therapy.

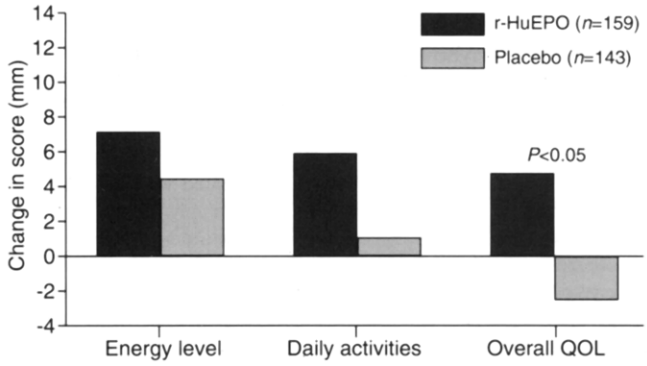

Fig. 3. Change in quality of life measures comparing r-HuEPO-treated and placebo-treated patients: all studies combined. (Reproduced by permission from *Blood Cell Growth Factors: Their Present and Future Use in Hematology and Oncology. Proceedings of the Beijing Symposium.* Martin J. Murphy, Jr., ed. Dayton, Ohio: AlphaMed Press, 1991. *Acta Haematologica* 1992, 87, Suppl. 1, 4-11.)

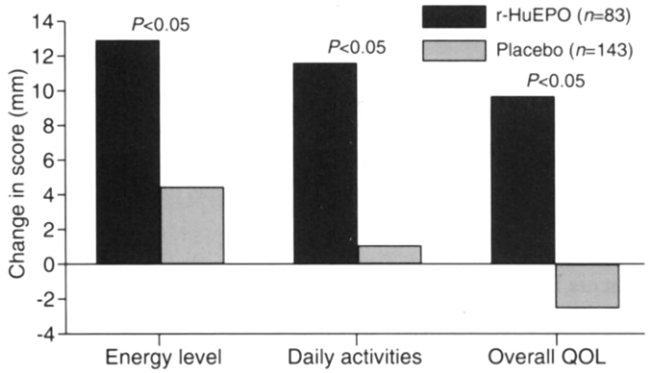

Fig. 4. Change in quality of life measures comparing all responders (haematocrit increase ≥6) in the r-HuEPO-treated groups with all placebo-treated patients. (Reproduced by permission from *Blood Cell Growth Factors: Their Present and Future Use in Hematology and Oncology. Proceedings of the Beijing Symposium.* Martin J. Murphy, Jr., ed. Dayton, Ohio: AlphaMed Press, 1991. *Acta Haematologica* 1992, 87, Suppl. 1, 4-11.)

*Table 11. Adverse experiences reported by ≥10% of patients**

Adverse event	r-HuEPO (%)	Placebo (%)
Nausea	23	29
Pyrexia	22	21
Asthenia	17	16
Fatigue	15	20
Vomiting	15	18
Diarrhoea	15	9
Oedema	14	8
Dizziness	10	9
Skin reaction at medication site	10	10
Constipation	10	9
Shortness of breath	8	15†
Decreased appetite	8	12
Trunk pain	8	12
Chills	7	10

*r-HuEPO $n=213$; placebo $n=200$. †Significantly ($P<0.03$) higher incidence for placebo. (Reproduced by permission from *Blood Cell Growth Factors: Their Present and Future Use in Hematology and Oncology. Proceedings of the Beijing Symposium.* Martin J. Murphy, Jr., ed. Dayton, Ohio: AlphaMed Press, 1991. *Acta Haematologica* 1992, 87, Suppl. 1, 4-11.)

DISCUSSION

The results of this double-blind, placebo-controlled study demonstrate the significant beneficial effect on haematocrit of r-HuEPO administered subcutaneously three times weekly at an appropriate dosage level. The average increase in haematocrit experienced by r-HuEPO-treated patients in the three trial groups ranged from 2.8 to 6.9%, achieving final average haematocrits of 32.1 to 35.5%. Placebo-treated patients, on the other hand, showed little change in haematocrit from baseline to final values, remaining in the 27.5 to 30.5% range. Increased haematocrit in r-HuEPO-treated patients vs. placebo-treated patients did not appear to be associated with differential transfusion practice between groups, nor with a differential intensity of chemotherapy.

This haematocrit improvement was accompanied by decreasing transfusion requirements after month 1 among r-HuEPO-treated patients receiving chemotherapy. The lack of any reduction in transfusion requirements after month 1 in the NC r-HuEPO-treated patients is possibly related to the relatively low dose of r-HuEPO used combined with the shorter follow-up time. Taken together, these data would suggest that when r-HuEPO is given in a dose of 150 U/kg subcutaneously three times weekly, transfusion requirements are reduced after the first month of therapy.

This stimulation of erythropoiesis in r-HuEPO-treated patients was reflected as a highly significant increase in the number of correctors and responders compared to the placebo-treated group. Within the three trial groups, 20.6 to 40.5% of the r-HuEPO-treated patients corrected their anaemia by achieving a haematocrit of ≥38% unrelated to transfusion, compared to a maximum of 4.1% of placebo-treated patients; 31.7 to 58.2% of the r-HuEPO groups had a haematocrit response ≥6% during the study, compared to a maximum of 13.5% in the placebo groups.

r-HuEPO appeared to be efficacious in a wide variety of tumour types. Patients with haematological or solid tumours appeared to respond equivalently to r-HuEPO, as did patients with or without evidence of tumour infiltration of the bone marrow. In addition, the significant improvement shown for quality-of-life measures in the r-HuEPO-treated responder subgroup suggests that r-HuEPO can substantially improve functional capacity in anaemic cancer patients when haematocrit increases significantly. This improvement is striking when one considers that the patient population under study was in the late stages of cancer, and that two of the three trial groups were enduring aggressive courses of cyclic chemotherapy.

r-HuEPO therapy was well-tolerated in this patient population, reflected in the similar nature and frequency of reported adverse experiences in the experimental and control patient groups. While statistical comparison of the treatment groups indicated no increased cardiovascular risk to r-HuEPO-treated patients, individual case histories suggest that occasional patients may experience increased blood pressure as haematocrit rises significantly above the baseline level. This is probably related to the fact that many of the patients in this study were older, and so may have had underlying recognised or unrecognised cardiovascular disease. The risk of hypertension, though, appears to be much less than among chronic renal failure patients [7].

CONCLUSIONS

r-HuEPO increases haematocrit and corrects anaemia in cancer patients whether or not they are receiving chemotherapy, and apparently without regard to type of cancer. In a dose of 150 U/kg three times weekly, r-HuEPO appears to decrease transfusion requirements after the first month of therapy, but not earlier. This therapy also appears to improve functional capacity in those anaemic cancer patients who show a significant increase in haematocrit in response to therapy, which is consistent with observations among chronic renal failure and AIDS patients [9,10]. r-HuEPO also appears to be well-tolerated in this patient population.

1. Bunn HF. Anemia associated with chronic disorders. In *Harrison's Principles of Internal Medicine,* 11th edition. New York, McGraw-Hill, 1987, 1504–1505.
2. Johnson RA and Roodman GD. Hematologic manifestations of malignancy. *Disease-A-Month* 1989, **35**,716–768.
3. Miller CB, Jones RJ, Piantadosi S, *et al.* Decreased erythropoietin response in patients with the anaemia of cancer. *N Engl J Med* 1990, **322**,1689–1692.
4. Walker RH. Special report: transfusion risks. *Am J Clin Pathol* 1987, **88**, 374–378.
5. Henry DH, Abels RI, Staddon AP, *et al.* Prospective evaluation of transfusion requirement in anemic cancer patients with or without chemotherapy. *Blood* 1990, **76** (Suppl. 1), 401a.
6. Eschbach JW, Egrie JC, Downing MR, *et al.* Correction of the anemia of end-stage renal disease with recombinant human erythropoietin. Results of a combined phase I and II clinical trial. *N Engl J Med* 1987, **316**, 73–80.
7. Winearls CG, Oliver DO, Pippard MJ, *et al.* Effect of human erythropoietin derived from recombinant DNA on the anaemia of patients maintained by chronic haemodialysis. *Lancet* 1986, **2**, 1175–1178.
8. Fischl M, Galpin JE, Levine JD, *et al.* Recombinant human erythropoietin for patients with AIDS treated with zidovudine. *N Engl J Med* 1990, **322**, 1488–1493.
9. Teehan B, Krantz S, Stone W, *et al.* Double-blind, placebo-controlled study of the therapeutic use of recombinant human erythropoietin for anemia associated with chronic renal failure in predialysis patients. *Am J Kid Dis* 1991, **28**, 50–59.
10. Data on file. R.W. Johnson Pharmaceutical Research Institute, Raritan, New Jersey, U.S.A.

Eur J Cancer, Vol. 29A, Suppl. 2, pp. S8-S12, 1993
Printed in Great Britain

0964-1947/93 $6.00+0.00

Erythropoietin Treatment of Chronic Anaemia of Cancer

H. Ludwig, C. Leitgeb, E. Fritz, M. Krainer, I. Kührer, G. Kornek, P. Sagaster and A. Weißmann

INTRODUCTION

CHRONIC ANAEMIA of cancer occurs in association with solid tumours, lymphomas, and haematological malignancies, although the specific incidence varies with the type of cancer. The probability of chronic anaemia developing generally increases with the duration of the disease, with patients in the advanced stages of malignancy being the most prone to the chronic anaemia of cancer [1]. Once anaemia has become chronic, the chances of overcoming it are slight. Because chronic anaemia results in weakness, fatigue, drowsiness, lethargy, depression and, in extreme situations, respiratory distress and cardiac decompensation, this relatively common problem in cancer patients can significantly impair their quality of life.

Currently, patients suffering from the chronic anaemia of cancer must rely on periodic blood transfusions. Blood transfusions, however, do not sufficiently counter the

Correspondence to H. Ludwig at the 1st Department of Medicine and Oncology, Wilhelminenspital, Vienna, Austria.
Revised 1 Mar. 1993; accepted 17 Mar. 1993.