Recombinant Human Erythropoietin (r-HuEPO) for the Treatment of the Anemia of Cancer

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Abstract. Advanced cancer is frequently associated with a significant anemia that may be due to the disease itself or the effect of concomitantly administered chemotherapeutic agents. In a series of double-blind, placebo-controlled trials, three populations of anemic cancer patients were randomized to r-HuEPO or placebo. The three populations were: a) patients not receiving concomitant chemotherapy, b) patients receiving chemotherapeutic regimens which did not contain cisplatin, and c) patients receiving chemotherapeutic regimens which contained cisplatin. In the no-chemotherapy trials, patients were treated with r-HuEPO (100 U/kg) or placebo SC 3 ×/wk for up to 8 weeks. In the two types of chemotherapy trials, patients were treated with r-HuEPO (150 U/kg) or placebo SC 3 ×/wk for 12 weeks.

A total of 413 patients were enrolled in these trials (124 in the no-chemotherapy group, 157 in the no-cisplatin chemotherapy group and 132 in the cisplatin chemotherapy group). In each trial, patients randomized to r-HuEPO had a significantly ($p < .004$) greater increase in hematocrit than placebo-treated patients. In the two types of chemotherapy trials combined, utilizing an r-HuEPO dose of 150 U/kg, r-HuEPO-treated patients had significantly ($p \leq .009$) lower transfusion requirements (percent of patients transfused and mean units of blood transfused per patient) than placebo-treated patients during months 2 and 3, but not during month 1. Quality of life parameters measured on a 100 mm visual analog scale significantly ($p < .05$) improved in r-HuEPO-treated patients whose hematocrit increased ≥ 6 percentage points compared with corresponding quality of life changes in placebo-treated patients. r-HuEPO was well tolerated compared with placebo.

The above results suggest that r-HuEPO may be a useful agent to palliate the morbid consequences of the anemia that is often found in association with advanced cancer.

Introduction

Advanced cancer is frequently associated with anemia which can significantly contribute to overall morbidity in these patients. The anemia found in

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cancer patients is often multifactorial in origin. Significant causes of anemia in cancer patients include blood loss from mucosal surfaces, deficiency of erythropoietic cofactors such as iron or folic acid, immune or nonimmune hemolysis, and tumor infiltration of the bone marrow. Frequently, however, anemia in cancer patients is characterized as the anemia of chronic disease (ACD) [1]. The ACD is a hypoproliferative anemia found in a wide variety of chronic infectious, inflammatory and neoplastic conditions. The ACD is characterized by erythroid hypoplasia of the bone marrow, slightly decreased red cell survival, decreased reticulocytosis, hypoferremia, and inappropriately low serum erythropoietin (EPO) levels for the degree of anemia [1-4]. Although patients with the ACD have decreased levels of circulating iron, they often have normal or increased amounts of iron in the bone marrow which cannot be used to support hemoglobin synthesis. The cause of this iron "blockade" is unclear, but it may be related to release of iron-binding proteins, such as lactoferrin, from neutrophils in response to inflammatory mediators such as IL-1 [2, 5]. Lactoferrin, and other proteins with a high affinity for iron, may then preferentially shuttle iron to macrophage storage sites, making it unavailable to support hemoglobin synthesis [2, 5]. Whatever the precise pathogenesis of the ACD, it has been successfully treated with rHuEPO in rheumatoid arthritis patients and in HIV-infected patients not receiving concomitant AZT (zidovudine) therapy [6, 7].

In addition to the above mechanisms for anemia in cancer patients, red cell production may be further suppressed by chemotherapeutic agents which may inhibit maturation of erythroid lineage cells in the bone marrow. Moreover, severe anemia may be found in cancer patients treated with the nephrotoxic agent cisplatin, which has been postulated to impair the ability of the kidneys to secrete EPO in response to anemia [8].

Since the anemia associated with cancer may be associated with inappropriately low serum EPO levels for the degree of anemia [9], and because the ACD has been successfully treated with r-HuEPO, r-HuEPO may be a rational therapy for anemia in cancer patients. This paper will describe the effect of r-HuEPO on anemia in three separate populations of cancer patients. These populations include: a) patients who were not receiving concomitant chemotherapy, b) patients who were receiving therapy with chemotherapeutic regimens not containing cisplatin, and c) patients who were receiving therapy with chemotherapeutic regimens containing cisplatin. Three separate trials were performed within each study population. However, all trials within each study population were analyzed as a single unit due to their essentially identical design.

Materials and Methods

Patients

In order to be enrolled in these trials, patients were to have any type of histologically-documented advanced cancer except for acute leukemia or cancer derived from the myeloid cell line. The performance score was to be between 0

and 3 by the ECOG Scale; life expectancy was to be at least 3 mos; patients were to be clinically stable for at least 1 mo prior to study participation and were required to be at least 18 yrs of age. In the two types of chemotherapy trials, the patients were to receive cyclic chemotherapy for up to 5 days every 3 - 4 wks.

Required laboratory values included: hemoglobin/hematocrit <10.5 g/dl or 32%, respectively, to document prestudy anemia, neutrophils >500 cell/μl, platelets >75,000 cells/μl (25,000 cells/μl in the no-chemotherapy trials), serum creatinine <2 mg/dl, negative direct Coombs test and no occult blood in the stool. Significant exclusion criteria included organ dysfunction not secondary to malignancy, cerebral metastases, uncontrolled hypertension, iron, folate or Vitamin B12 deficiency, acute illness within 7 days of study participation and experimental therapy within 30 days of study participation.

Study Protocol

Patients enrolled in the no-chemotherapy trial were randomized to r-HuEPO 100 U/kg or a comparable volume of placebo s.c. 3 times per week for 8 weeks or until a hematocrit of 38 - 40% was attained. Patients enrolled in the two types of chemotherapy trials were randomized to r-HuEPO 150 U/kg or a comparable volume of placebo s.c. 3 times per week for 12 weeks or until a hematocrit of 38 - 40% was attained, after which the dose of study medication was titrated to maintain the hematocrit within the target range. After completion of the double-blind phase of these studies, open-label therapy with r-HuEPO was permitted, but this report will describe only the results of double-blind therapy.

Analytic Technique

The major efficacy criteria pertained to the effects of study medication on hematocrit, transfusion requirements and quality of life. For the purpose of these studies, "correction of anemia" was defined as attainment of a hematocrit ≥38% unrelated to transfusion, and "response to therapy" was defined as an increase of hematocrit of at least 6 percentage points unrelated to transfusion. Transfusion requirements were categorized based on the percentage of patients transfused in each treatment group and the mean number of units of blood transfused per patient in each treatment group. Prior to and after completion of double-blind therapy, patients were asked to rate their energy level, ability to perform daily activities and overall quality of life on a 100 mm visual analog scale, the extremes of which represented the best possible and worst possible scores for that category. Changes from prestudy to poststudy in quality of life scores were compared in placebo-treated and r-HuEPO-treated patients to determine the effect of therapy on functional capacity. Patients were considered valid for efficacy analysis if they completed ≥15 days of study participation. All patients were considered valid for safety analysis.

Statistical inference was carried out using Fisher's Exact Test on dichotomous variables that were formulated as 2 × 2 tables, such as proportion of patients transfused by study month. For discrete data not formulated as 2 × 2 tables, the Extended Mantel-Haenszel test was used with integer scores. The

two-sample *t*-test was used for between-group comparison of means, and the paired *t*-test was used to test changes from baseline to final value. Where appropriate, a linear model approach was used, with treatment group as the design factor and various baseline measures, such as baseline hematocrit, endogenous EPO level, tumor involvement of the bone marrow and chemotherapy intensity (area under the neutrophil time curve), as covariates. All statistical tests of hypotheses were two-sided and carried out at the $\alpha = 0.05$ level.

r-HuEPO was supplied by the R.W. Johnson Pharmaceutical Research Institute (Raritan, NJ) in single use vials or ampules in a buffered solution containing human serum albumin 2.5 mg/ml. Placebo consisted of an identical buffered solution containing human serum albumin 2.5 mg/ml without added r-HuEPO.

All patients gave informed written consent prior to participating in these trials which were approved at each investigational site by an appropriately constituted institutional review board (IRB).

Results

Baseline Parameters

Baseline parameters are presented for patients enrolled across all three study types combined. Significant baseline differences between treatment groups will be mentioned as appropriate.

A total of 413 patients were enrolled in these studies; 124 were enrolled in the no-chemotherapy trials, 157 were enrolled in the no-cisplatin chemotherapy trials and 132 were enrolled in the cisplatin chemotherapy trials. A total of 213 patients were randomized to r-HuEPO, and 200 patients were randomized to placebo. Two hundred and six patients randomized to r-HuEPO were considered evaluable for efficacy, and 190 patients randomized to placebo were considered to be evaluable for efficacy (i.e., participated in trials for ≥ 15 days).

Table I presents demographic characteristics for patients enrolled in these trials. Approximately equivalent numbers of males and females were enrolled. The patients were mainly Caucasian and had a mean age of approximately 62 years. The mean baseline weight of approximately 67 kg suggests that the patients were not grossly wasted at study entry.

Table II presents additional baseline characteristics for patients enrolled in these trials. During the baseline period (the 2 months prior to study participation for the no-chemotherapy trials and the 3 months prior to study participation for the 2 types of chemotherapy trials), 45% of r-HuEPO-treated patients and 48% of placebo-treated patients received RBC transfusions. The mean number of units of blood transfused per patient per month during the baseline period was 0.67 in the r-HuEPO group and 0.73 in the placebo group. The mean hematocrit immediately prior to study participation was 29.1% in r-HuEPO-treated patients and 28.5% in the placebo-treated patients. These baseline hematocrits were

Table I. Demographics

Parameter	r-HuEPO (N = 213)	Placebo (N = 200)
Sex		
Male	102	95
Female	111	105
Race		
Caucasian	179	172
Others	34	28
Age (years)	61.2	62.5
Height (inches)	66.5	66.2

Table II. Baseline characteristics

Parameter	r-HuEPO	Placebo
Percent transfused	44.7	48.4
Mean Units Transfused/Patient/Month	0.67	0.73
Mean Hematocrit (%)	29.1	28.5
Mean Neutrophil Count (Cells/μL)	4163	4017
Endo Serum EPO Level mU/ml		
Mean	146	149
Median	76	85
Mean Overall Quality of Life (mm on a 100 mm scale)	50.0	50.4

probably somewhat inflated due to the effect of prior red cell transfusions. Finally, the prestudy overall quality of life score was approximately 50 mm out of a possible 100 mm indicating that the enrolled patients had significant limitation of their functional capacity at baseline evaluation.

Figure 1 presents the distribution of endogenous serum EPO levels at baseline. In general, serum EPO levels tended to be low or appropriate for the baseline hematocrit. Approximately 75% of patients had endogenous serum EPO levels ≤150 mU/ml, and fewer than 5% of patients had baseline endogenous serum EPO levels >500 mU/ml. The median endogenous EPO levels in the no-chemotherapy and no-cisplatin chemotherapy trials were 89.5 and 94.5 mU/ml, respectively, whereas the median baseline endogenous EPO level in the cisplatin-treated patients was 54 mU/ml, which was significantly ($p < .05$) lower than in the no-chemotherapy and no-cisplatin chemotherapy populations.

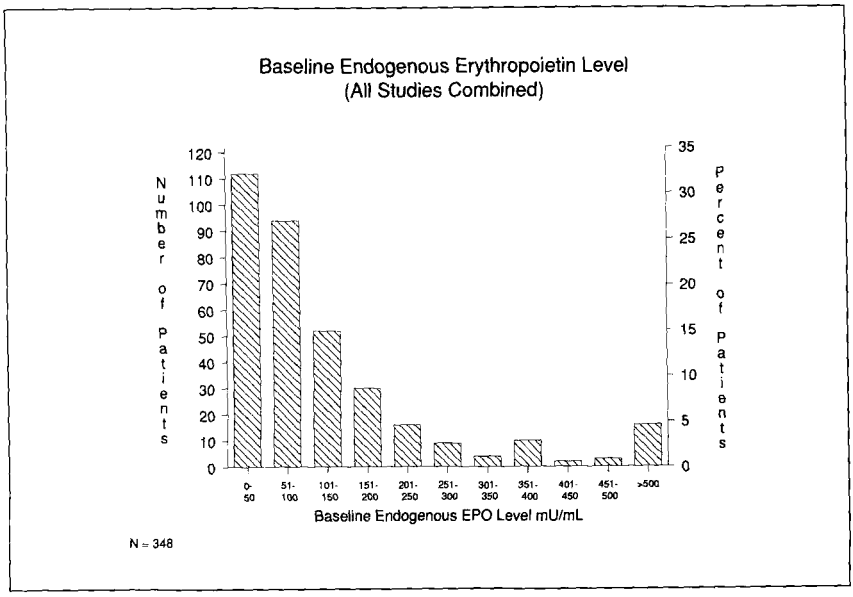

Fig. 1. Distribution of baseline endogenous serum EPO levels pooled across all trials. Baseline serum EPO levels available for 348 patients.

Table III. Distribution of tumor types

Tumor Type	Percent r-HuEPO	Percent Placebo
Hematologic	32.0	32.1
Non-Hematologic	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
Gynecologic	9.2	12.1
Lung, small cell	3.9	7.9
Head and neck	2.4	1.6
Esophagus	1.0	1.6
Unknown primary site	3.4	1.1
Others	5.8	7.9

Table III gives the histologic origin of tumors for patients randomized to r-HuEPO and placebo. As is evident, patients participating in these trials had a wide variety of different tumor types. However, the distribution of tumor types

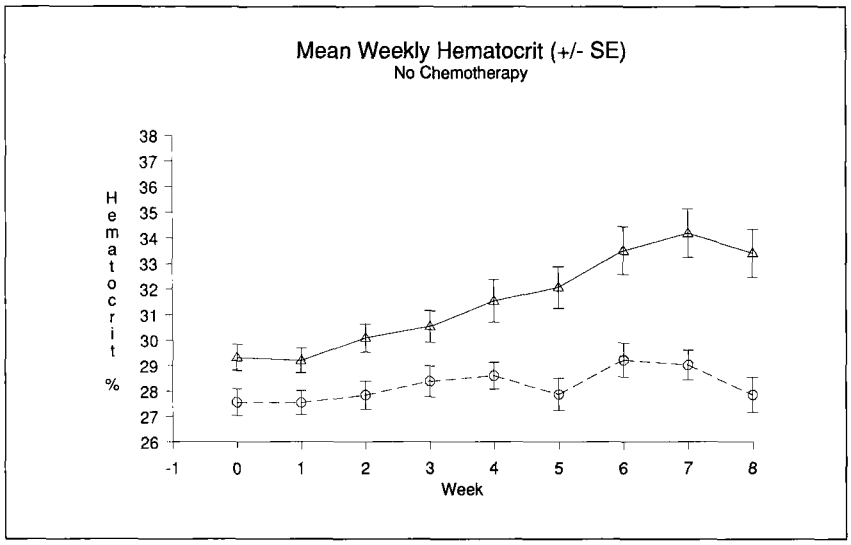

Fig. 2. Mean weekly hematocrit ± SE in r-HuEPO- and placebo-treated patients in no-chemotherapy trials. ▲ = r-HuEPO (100 U/kg); ● = placebo.

was relatively similar in patients randomized to r-HuEPO and placebo. Overall, approximately 32% of the patients had hematologic tumors (e.g., lymphoma, multiple myeloma or chronic lymphocytic leukemia), and approximately 68% of patients had solid tumors, the distribution of which is given in Table III.

Within each set of trials, the baseline characteristics of patients randomized to r-HuEPO and placebo were similar. The most notable difference occurred for hematocrit in the non-chemotherapy trials which was significantly ($p < .05$) higher in patients randomized to r-HuEPO than in patients randomized to placebo (29.3% and 27.6%, respectively).

Effect on Hematocrit

Figures 2, 3 and 4 present mean weekly hematocrit in r-HuEPO-treated and placebo-treated patients over the course of therapy. As is apparent, the mean weekly hematocrit increased progressively in the r-HuEPO-treated patients in all three study types, whereas the mean weekly hematocrit remained essentially unchanged in the placebo-treated patients.

Table IV presents the change in hematocrit from baseline to final value in r-HuEPO- and placebo-treated patients in each of the three study types. The change in hematocrit from baseline to final value was significantly ($p < .004$) greater in r-HuEPO-treated patients compared with the corresponding response in placebo-treated patients in each study type. Table V presents the percentage of patients in each treatment group whose anemia was corrected (i.e., Hct ≥38% unrelated to transfusion) or who responded to therapy (i.e., Hct increased ≥6 percentage points unrelated to transfusion). Within each study type, a significantly

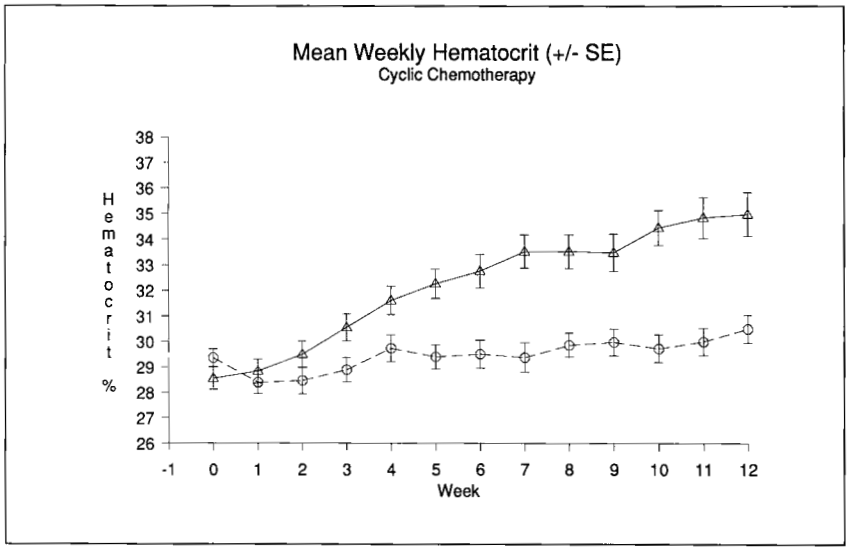

Fig. 3. Mean weekly hematocrit ± SE in r-HuEPO- and placebo-treated patients in cyclic (non-cisplatin-containing) chemotherapy trials. ▲ = r-HuEPO (150 U/kg); ● = placebo.

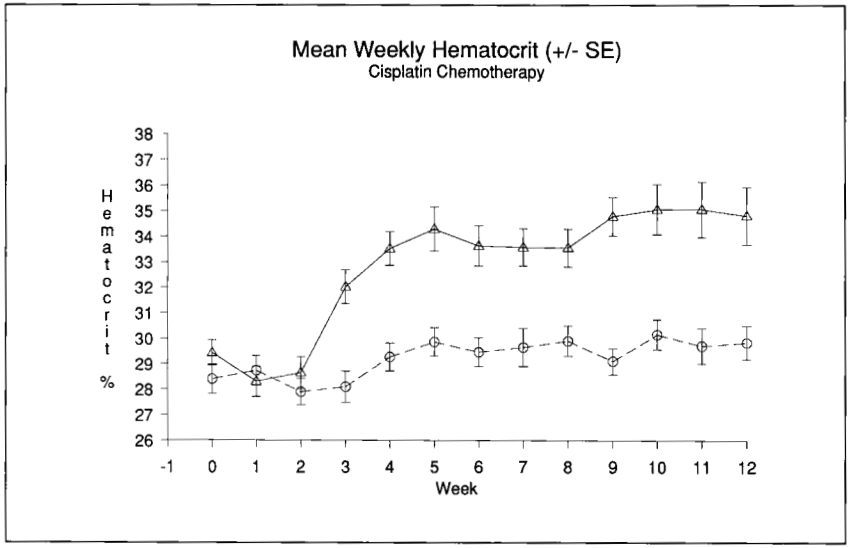

Fig. 4. Mean weekly hematocrit ± SE in r-HuEPO- and placebo-treated patients in cyclic cisplatin chemotherapy trials. ▲ = r-HuEPO (150 U/kg); ● = placebo.

Table IV. Change in hematocrit from baseline to last value

Treatment	N	Baseline Value (%)	Final Value (%)	Percentage Point Change
No-Chemo				
r-HuEPO	63	29.3	32.1	2.8*
Placebo	55	27.6	27.5	-0.1
Chemo				
r-HuEPO	79	28.6	35.5	6.9*
Placebo	74	29.4	30.5	1.1
Cisplatin				
r-HuEPO	64	29.4	35.4	6.0*
Placebo	61	28.4	29.7	1.3

* Significantly ($p < 0.004$) greater than placebo response.

Table V. Correction of anemia/response to therapy unrelated to transfusion

		Percent of Patients	
Study Type/ Treatment Group	N	Correctors (Hct >38%)	Responders (Hct Increase >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

($p < .008$) greater proportion of r-HuEPO-treated patients achieved correction of anemia and responded to therapy compared with the corresponding proportion in placebo-treated patients. Finally, Table VI presents hematocrit response by specific tumor type for several common tumors in r-HuEPO- and placebo-treated patients pooled across all trials. The hematocrit response to r-HuEPO appears to be relatively similar in patients with hematologic and solid cancers. The relatively small hematocrit increase in r-HuEPO-treated patients with prostate cancer (2.3 percentage points) may be related to the fact that most of these

Table VI. Change in hematocrit from baseline to final value in various tumor types

	r-HuEPO			Placebo		
Tumor Types	N	Baseline Hct(%)	Change in Hct(%)	N	Baseline Hct(%)	Change in Hct(%)
CLL 7	29.5	6.0[a]	9	29.7	0.9	
Myeloma	19	29.8	3.7[b]	23	28.7	0.3
Lymphoma	40	29.5	6.0[c]	29	29.5	0.5
Breast Cancer	22	28.4	6.5[c]	24	29.3	1.6
Lung Cancer*	29	29.2	6.4[c]	32	28.6	1.1
Prostate Cancer	23	28.3	2.3	17	27.2	0.1
GI Cancer	21	28.2	5.8[c]	10	28.3	1.6
Gynecologic Cancer	18	28.8	7.7[c]	23	28.0	-0.3

* small cell and non-small cell combined
[a] p-value = 0.0776 for difference between r-huEPO and placebo
[b] p-value = 0.0581 for difference between r-HuEPO and placebo
[c] statistically significant ($p \leq 0.05$) difference between r-HuEPO and placebo

patients were treated in the no-chemotherapy trials using a relatively modest r-HuEPO dose of 100 U/kg and a duration of therapy of only 8 weeks.

Overall, it appeared that r-HuEPO can increase hematocrit compared with placebo in cancer patients without regard to whether or not patients were receiving chemotherapy, the type of chemotherapy administered, or the specific type of tumor treated.

Transfusion Requirements

Baseline transfusion requirements were similar ($p > .05$) in r-HuEPO- and placebo-treated patients in the three study types (data not shown). Table VII shows on-study gross mean transfusion requirements in r-HuEPO- and placebo-treated patients in each of the three study types. Within each study type, the proportion of patients transfused with red cells was lower in the r-HuEPO-treated patients than the corresponding proportion in placebo-treated patients, but the differences were not statistically significant ($p > .05$). In a similar manner, the mean number of units of blood transfused per patient in each study type was lower in the r-HuEPO-treated patients than in the corresponding placebo group, but the differences were also not statistically significant ($p > .05$). Interestingly, the largest transfusion requirements were found in cisplatin-treated patients (Table VII).

Since there is a discrete lag phase before the effect of r-HuEPO becomes evident on erythropoiesis, it was hypothesized that r-HuEPO would be most likely to reduce transfusion requirements during the latter phase of therapy and would be least likely to reduce transfusion requirements during the early phase of therapy, particularly during the first month of therapy. Table VIII gives linear

Table VII. Transfusion requirements in r-HuEPO- and placebo-treated patients over entire course of trials

Population	N	Proportion of Patients Transfused(%)	Mean Units of Blood Transfused Per Patient
No Chemotherapy			
r-HuEPO	63	33.3	1.52
Placebo	55	38.2	2.19
Chemotherapy			
r-HuEPO	79	40.5	2.03
Placebo	74	48.6	2.75
Cisplatin Chemotherapy			
r-HuEPO	64	53.1	3.56
Placebo	61	68.9	4.01

Table VIII. Transfusion requirements in chemotherapy trials by months on study

		Month 1		*Months 2 and 3*		
Group	N	(%) Trans-fused[a]	Units Trans-fused/Pt[b]	N	(%) Trans-fused[a]	Units Trans-fused/Pt[b]
Chemotherapy						
r-HuEPO	79	25.3	0.69	70	28.6	0.91
Placebo	74	27.0	0.71	68	36.8	1.65 (p=.056)
Cisplatin						
r-HuEPO	64	43.8	1.71	56	26.8	1.20
Placebo	61	44.3	1.20	55	56.4 (p<.005)	2.00 (p=.089)
Chemotherapy & Cisplatin Combined						
r-HuEPO	143	33.6	1.09	126	27.8	1.04
Placebo	135	34.8	0.98	123	45.5 (p<.005)	1.81 (p=.009)

[a] Comparison with placebo performed by Fisher's Exact Test
[b] Comparison with placebo performed by t-test

model transfusion requirements in the two types of chemotherapy trials stratified by months on therapy, month 1 versus months 2 and 3 combined. As is evident from Table VIII, transfusion requirements were similar in r-HuEPO- and placebo-treated patients during month 1, but transfusion requirements were substantially lower in r-HuEPO-treated patients than in placebo-treated patients

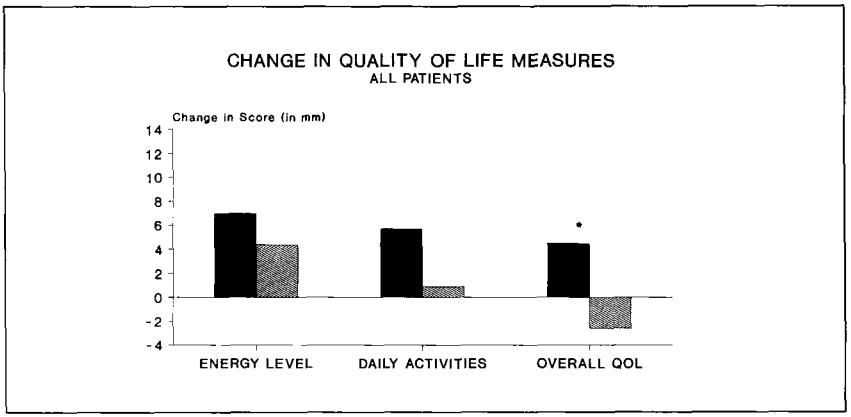

Fig. 5. Change (in mm) in quality-of-life measures from baseline to final evaluation in r-HuEPO- and placebo-treated patients pooled across all trials for patients having baseline and final values recorded. ■ = r-HuEPO (N = 159); ▒ = placebo (N = 143). * Significantly ($p < 0.05$) different than corresponding placebo response.

during months 2 and 3. When the data from the chemotherapy trials were combined, transfusion requirements were significantly ($p \leq .009$) lower in r-HuEPO-treated patients than in placebo-treated patients during months 2 and 3, supporting the conclusion that r-HuEPO in a dose of 150 U/kg 3 times/week can reduce transfusion requirements after the first month of therapy, but not during the first month of therapy. A similar pattern of decreased transfusion requirements after the first month of therapy was not observed in the no-chemotherapy trials (data not shown). However, it is possible that failure to note reduced transfusion use in r-HuEPO-treated patients after the first month of therapy in this patient population may have been related to the relatively low dose of r-HuEPO employed (100 U/kg) and the relatively short duration of follow-up (8 weeks) compared with the chemotherapy trials (using an r-HuEPO dose of 150 U/kg and a follow-up of 12 weeks).

Quality of Life

Figure 5 presents changes from baseline to final evaluation for quality of life scores in r-HuEPO- and placebo-treated patients pooled across all study types. Quality of life scores improved in r-HuEPO-treated patients from prestudy to poststudy compared with the corresponding changes in placebo-treated patients, but the differences were small and statistically significant only for the overall quality of life assessment.

Figure 6 presents changes in quality of life scores in r-HuEPO-treated responders (i.e., in patients whose Hct increased ≥ 6 percentage points unrelated to transfusion) and placebo-treated patients. In contrast to the r-HuEPO-treated population as a whole, the changes in quality of life scores in r-HuEPO-treated responders were significantly ($p < .05$) greater than the corresponding changes

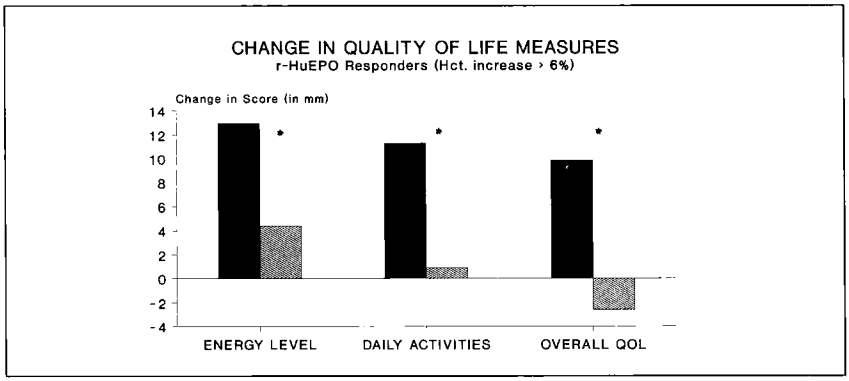

Fig. 6. Change (in mm) in quality-of-life measures from baseline to final evaluation in r-HuEPO-treated responders (i.e., Hct increased ≥ 6%) and placebo-treated patients pooled across all trials for patients having baseline and final evaluations recorded. ■ = r-HuEPO (N=83); ▨ = placebo (N = 143).* Significantly ($p < 0.05$) different than corresponding placebo response.

in placebo-treated patients. Moreover, quality of life scores in r-HuEPO-treated responders improved about 24% from baseline values (approximately 47 mm out of a possible 100 mm) despite the presence of advanced cancer and administration of cyclic chemotherapy in approximately three quarters of the responding population. Taken together, these data would suggest that functional capacity improves in r-HuEPO-treated cancer patients whose hematocrit increases significantly (e.g., ≥ 6 percentage points) during the course of therapy.

Effect of Tumor Type and Tumor Infiltration of the Bone Marrow on Response to r-HuEPO Therapy

Thirty-two percent of r-HuEPO-treated patients had hematologic tumors, and 68% had solid tumors. Thirty-four percent of r-HuEPO-treated responders (i.e., patients whose hematocrit increased ≥6% unrelated to transfusion) had hematologic tumors, and 66% had solid cancers. The equivalent distribution of r-HuEPO-treated patients with hematologic and solid tumors in the r-HuEPO-treated population as a whole and in the r-HuEPO-treated responder population suggests that patients with hematologic and solid cancers respond equivalently to r-HuEPO therapy. This conclusion is also supported by data presented in Table VI.

Twenty-eight percent of r-HuEPO-treated patients were considered to have baseline evidence of tumor infiltration of the bone marrow, based on review of available clinical data. Twenty-six percent of the r-HuEPO-treated responder population had baseline evidence of tumor infiltration of the bone marrow. The similar distribution of patients with baseline evidence of tumor infiltration of the bone marrow in the r-HuEPO-treated population taken as a whole and in the r-HuEPO-treated responder population suggests that patients with tumor infiltra-

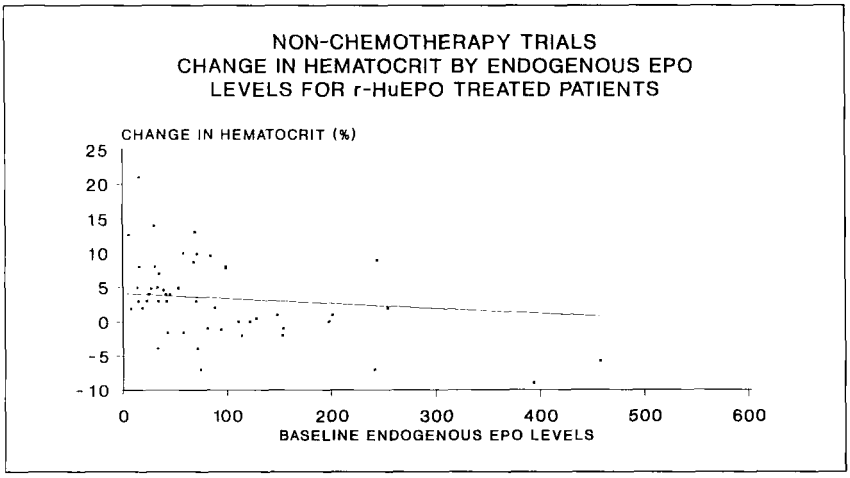

Fig 7. Change in hematocrit from baseline to final evaluation versus baseline endogenous serum EPO level (mU/ml) for r-HuEPO-treated patients in no-chemotherapy trials. — = regression line; $Y = 4.12 \leq 0.0072X$.

tion of the bone marrow respond to r-HuEPO therapy similarly to patients without tumor infiltration of the bone marrow.

Effect of Endogenous Serum EPO Level on Response to Therapy

In the no-chemotherapy trials, multivariate statistical analysis indicated that the response to r-HuEPO therapy (change in hematocrit from baseline to final value) varied inversely with the baseline endogenous EPO level (Fig. 7). The hematocrit response to r-HuEPO therapy was significantly greater than the hematocrit response in placebo-treated patients for serum EPO levels up to 174 mU/ml.

In the two types of chemotherapy trials, multivariate statistical analysis indicated that there was not a statistically significant relationship between hematocrit response to r-HuEPO therapy and baseline endogenous serum EPO levels.

Transfusion Trigger and Intensity of Chemotherapy

In order to ensure that the hematocrit results reported above were not related to differential transfusion practice in r-HuEPO- and placebo-treated patients, the hematocrit at the time of transfusion in r-HuEPO- and placebo-treated patients was determined. In each of the study types, the mean hematocrit at the time of transfusion in r-HuEPO- and placebo-treated patients was in the 24 - 25% range. Thus, it is unlikely that the results reported above were related to differential transfusion practice in the r-HuEPO- and placebo-treated groups.

The intensity of chemotherapy in the r-HuEPO-treated and placebo-treated patients in the two types of chemotherapy trials was also compared to ensure

Table IX. Intensity of chemotherapy (patients evaluable for efficacy in the chemotherapy and cisplatin studies)

	Chemotherapy		Cisplatin Chemotherapy	
Parameter	r-HuEPO (N = 79)	Placebo (N = 74)	r-HuEPO (N = 64)	Placebo (N = 61)
AUC (cells × wk/μL)[a]	30,203	34,189	33,289	33,453
Number (%) of patients with ANC <1000 cells/μL[b]	51 (64.6)	48 (64.9)	53 (82.8)	47 (77.0)
Number (%) of patients with ANC <500/μL	32 (40.5)	23 (31.1)	38 (59.4)	30 (49.2)
Platelets/μL-change from baseline to final value $\times 10^3$	−39.0	−48.0	−101.2	−97.3
Number (%) of patients with platelets <50,000/μL	18 (22.8)	17 (23.0)	23 (35.9)	21 (34.4)
Number (%) of patients with platelets <20,000/μL	2 (2.5)	2 (2.7)	7 (10.9)	4 (6.6)
Total Cisplatin dose (mg)	-	-	272.9	294.4

[a]area under the curve
[b]area under the neutrophil time curve
No statistically significant ($p > .05$) differences between r-HuEPO response and corresponding placebo response.

that the reported hematocrit responses were not related to differential intensity of chemotherapy. Since patients in the two types of chemotherapy studies received a wide variety of different chemotherapeutic regimens, it was considered best to use a surrogate marker for the intensity of chemotherapy. The most appropriate surrogate marker for the intensity of chemotherapy, particularly for the intensity of chemotherapy-induced myelosuppression, appeared to be the effect of chemotherapy on the absolute neutrophil count (ANC). The effect of chemotherapy on platelet counts was also used as an additional marker for the intensity of chemotherapy-induced myelosuppression (no hematopoietic growth factors other than EPO were administered in these trials). In addition, in the cisplatin trial, the total dose of cisplatin administered to the r-HuEPO- and placebo-treated patients was compared. The data presented in Table IX suggest that the effect of chemotherapy on neutrophil and platelet counts was similar in r-HuEPO- and placebo-treated patients; in addition, the total dose of cisplatin administered to r-HuEPO-treated and placebo-treated patients was similar. Taken together, these data suggest that r-HuEPO- and placebo-treated patients received chemotherapeutic regimens of similar intensity, making it unlikely that the results described above were related to differential intensity of chemotherapy.

Table X. Adverse experiences reported >10% of patients in either treatment group

	Percent of Patients	
Adverse Event	r-HuEPO (N = 213)	Placebo (N = 200)
Nausea	23	29
Pyrexia	22	21
Asthenia	17	16
Fatigue	15	20
Vomiting	15	18
Diarrhea	15	9
Edema	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

* Significantly higher incidence for placebo patients ($p < 0.030$)

Safety

r-HuEPO appeared to be tolerated well compared with placebo in these trials. Seventy-four percent of r-HuEPO-treated patients completed double-blind therapy compared with 73% of placebo-treated patients. Seventeen percent of r-HuEPO-treated patients discontinued double-blind therapy due to an adverse experience, death or disease progression versus 14% of placebo-treated patients who dis-continued double-blind therapy for these reasons. Fifteen percent of r-HuEPO-treated patients died on study or within 30 days of study completion compared with 16% of placebo-treated patients. Finally, the distribution of performance scores was similar ($p > .05$) at baseline and final evaluation in r-HuEPO- and placebo-treated patients (data not shown). Taken together, these data would suggest that r-HuEPO did not adversely effect outcome in the treated population.

Hypertension was noted as an adverse experience in 5.2% of r-HuEPO-treated patients and in 3.5% of placebo-treated patients. Although the difference was not statistically significant, individual case histories suggest that there may be some risk of hypertension in cancer patients who experience a significant increase in hematocrit in response to r-HuEPO therapy. Seizures were noted in 5 (2.4%) r-HuEPO-treated patients and in 4 (2.0%) placebo-treated patients. Seizures in 2 of the r-HuEPO-treated patients occurred in the context of a signifi-

cant increase in hematocrit and blood pressure from baseline values. However, these patients also had evidence of central nervous system pathology (e.g., cerebral metastases) which may have contributed to the reported convulsive events. Thrombotic events (e.g., cerebrovascular accident, pulmonary embolism) occurred in 6.1% of r-HuEPO-treated patients and in 5.5% of placebo-treated patients.

Table X gives adverse experiences reported by 10% of patients in either treatment group. There were no statistically significant differences in the incidence of adverse experiences reported between groups, except for shortness of breath which occurred in a higher incidence in placebo-treated patients. No antibodies against r-HuEPO developed during the course of therapy. Variations in clinical laboratory parameters were similar in r-HuEPO- and placebo-treated patients.

Discussion

Advanced cancer is frequently associated with a clinically significant anemia, which may be related to the disease itself or to the effect of concomitantly administered chemotherapeutic agents. Previous work by *Miller et al.* has demonstrated that serum EPO levels are lower in cancer patients than in patients with uncomplicated iron deficiency anemia [9]. This suggests that anemia in cancer patients may be at least partly due to a blunted EPO response to a decreased red cell mass. For the patients reported here, the median serum EPO level was lower in patients who were being treated with cisplatin than in patients who were not being treated with cisplatin, although baseline hematocrits were similar. Although speculative, it is possible that this difference may be related to the nephrotoxic effect of cisplatin.

A total of 413 cancer patients with anemia due to their disease or concomitantly administered chemotherapy were enrolled in these trials. Patients whose anemia appeared to be due to other factors such as iron deficiency or hemolysis were excluded. Three distinct patient populations were studied. These were: a) patients who were not being treated with chemotherapy, b) patients who were being treated with cyclic chemotherapy regimens that did not contain cisplatin, and c) patients who were being treated with chemotherapy regimens containing cisplatin. Cisplatin was selected for separate study because it is a frequently used agent that often causes significant anemia [10].

The results presented above indicate that r-HuEPO can increase hematocrit and correct anemia in all three patient populations studied in short-term trials lasting up to 12 weeks. Responsiveness to r-HuEPO appeared to be equivalent in patients with hematologic and solid cancers as well as in patients with or without tumor infiltration of the bone marrow. When r-HuEPO was administered in a dose of 150 U/kg 3 times per week, there was a reduction in red cell transfusion requirements after the first month of therapy, but not during the first

month of therapy. The hazards of blood transfusion are well known (e.g., transmission of viral agents), and the benefit of reducing the need for transfusion needs no elaboration. In addition, quality of life scores measured by visual analog scale significantly improved in r-HuEPO-treated patients who had a substantial hematocrit response to therapy compared with corresponding changes in quality of life scores in placebo-treated patients. These data, which are consistent with data from anemic, predialysis patients with chronic renal failure and AZT (zidovudine)-treated AIDS patients, indicate that increased functional capacity is most noticeable in anemic patients who have a significant hematocrit response to r-HuEPO therapy [7, 15].

Response to r-HuEPO therapy in patients receiving no chemotherapy was inversely related to the baseline endogenous serum EPO level. This is consistent with data previously reported for anemic, AZT (zidovudine)-treated AIDS patients [11]. However, there was no significant relationship between the response to r-HuEPO and the baseline endogenous EPO level in cancer patients receiving cyclic chemotherapy. It has recently been shown that serum EPO levels may temporarily rise after administration of intense chemotherapy with a slow return to baseline (or sub-baseline) levels thereafter [12, 13, 14]. Consequently, it is possible that failure to find a significant relationship between baseline endogenous serum EPO levels and response to r-HuEPO therapy may have been due to fluctuation of prestudy serum EPO levels related to prior cycles of chemotherapy, but this is speculative. The hematocrit response to r-HuEPO therapy did not appear to be related to differential transfusion practice in r-HuEPO-treated and placebo-treated patients. In addition, it appeared that r-HuEPO- and placebo-treated patients received chemotherapy regimens of comparable myelosuppressive intensity based on similar effects on the neutrophil and platelet counts in the r-HuEPO- and placebo-treated populations. Moreover, in the cisplatin trials, equivalent total doses of cisplatin were administered to r-HuEPO- and placebo-treated patients. Consequently, it is unlikely that the results described herein were related to differential intensity of chemotherapy in the r-HuEPO- and placebo-treated populations.

r-HuEPO was tolerated well in these trials. Based on a similar percentage of patients in the r-HuEPO and placebo groups who prematurely discontinued therapy due to death, adverse experience or disease progression as well as the comparable distribution of prestudy and poststudy performance scores and percentage of patients who died within 30 days of study completion in the r-HuEPO and placebo groups, r-HuEPO did not appear to have a deleterious effect on outcome in the treated population. Although the risk of hypertension in r-HuEPO-treated cancer patients appears to be lower than in chronic renal failure patients, hypertension may occasionally occur in r-HuEPO-treated cancer patients as the hematocrit rises significantly above baseline values. This may be related to the generally advanced age of these patients or to the presence of recognized or unrecognized underlying cardiorenal disease.

In summary, r-HuEPO therapy increased hematocrit and corrected anemia in cancer patients receiving no chemotherapy, in cancer patients receiving cyclic chemotherapeutic regimens not containing cisplatin, and in cancer patients receiving cyclic chemotherapeutic regimens containing cisplatin. When administered in a dose of 150 U/kg 3 times per week, transfusion requirements were lower in r-HuEPO-treated patients than in placebo-treated patients after the first month of therapy. Quality of life parameters measured by visual analog scale significantly improved in r-HuEPO-treated patients who had a significant hematocrit response to therapy compared with the corresponding responses in placebo-treated patients. r-HuEPO was generally well tolerated compared with placebo. Based on the above, r-HuEPO may be a useful therapy to palliate the significant anemia which may be related to advanced cancer or its therapy when other causes of anemia (such as iron deficiency) have been excluded.

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Oral Discussion

Dr. Peters: You indicate that some patients respond to erythropoietin therapy and some do not. Was there any correlation between the response to the chemotherapy program, the successive treatment of their disease, and the response to treatment with erythropoietin?

Dr. Abels: That is difficult to answer because we did not actually measure tumor status before and after therapy. I think though, that when you look at the data there were some patients in the placebo group who did respond to "therapy," and I presume that those responses may have been related to the efficacy of the chemotherapy.

Dr. Peters: The second issue is one that is a burning issue in the United States, and that is have you done any cost effectiveness studies? Erythropoietin is a relatively expensive molecule. Is it cost effective to do this?

Dr. Abels: Formal cost effectiveness studies are not available right now, but I think that there are certain medical benefits that are fairly obvious. I think patients do feel better when they are treated with erythropoietin and their hematocrits are increased. In addition, transfusion requirements may be reduced by treatment. Both of these outcomes are valuable. At this point, the individual physician, patient and third party payer have to put a value on what they think attainment of these benefits is worth, pending formal cost effectiveness studies.

Dr. Weeks: I was pretty impressed that there was only a 30 - 36% response rate with your erythropoietin in this patient population. Can you explain why it would be so low?

Dr. Abels: You have to remember that response is whatever you define it to be. We used an arbitrary definition of response which was an increase in hematocrit of at least 6 percentage points unrelated to transfusion. In the two chemotherapy trials over the 12-week course of observation the response rate was in the 50 - 60% range and not 35%. The response rate was about 32% in the no chemotherapy trial in the r-HuEpo-treated patients over an eight-week period of treatment. I presume, although I don't have the data available now, that if you continued therapy beyond 12 weeks you would increase the arbitrarily defined response rate to the 75-80% range, but that remains to be seen.

Errata:

Recombinant Human Erythropoietin (r-HuEPO) for the Treatment of the Anemia of Cancer by *R. I. Abels, K. M. Larholt, K. D. Krantz, E. C. Bryant*

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Table VI. Change in hematocrit from baseline to final value in various tumor types

		r-HuEPO			Placebo	
Tumor Types	N	Baseline Hct(%)	Change in Hct(%)	N	Baseline Hct(%)	Change in Hct(%)
CLL	7	29.5	6.0[a]	9	29.7	0.9
Myeloma	19	29.8	3.7[b]	23	28.7	0.3
Lymphoma	40	29.5	6.0[c]	29	29.5	0.5
Breast Cancer	22	28.4	6.5[c]	24	29.3	1.6
Lung Cancer*	29	29.2	6.4[c]	32	28.6	1.1
Prostate Cancer	23	28.3	2.3	17	27.2	0.1
GI Cancer	21	28.2	5.8[c]	10	28.3	1.6
Gynecologic Cancer	18	28.8	7.7[c]	23	28.0	-0.3

* small cell and non-small cell combined
[a] p-value = 0.0776 for difference between r-HuEPO and placebo
[b] p-value = 0.0581 for difference between r-HuEPO and placebo
[c] statistically significant ($p \leq 0.05$) difference between r-HuEPO and placebo

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Legend to Fig 7. Change in hematocrit from baseline to final evaluation versus baseline endogenous serum EPO level (mU/ml) for r-HuEPO-treated patients in no-chemotherapy trials. — = regression line; $Y = 4.12 - 0.0072X$.

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Oral Discussion

Dr. Peters: You indicate that some patients respond to erythropoietin therapy and some do not. Was there any correlation between the response to the chemotherapy program, the successful treatment of their disease, and the response to treatment with erythropoietin?