Recombinant Human Erythropoietin (rHuEPO) for the Treatment of the Anemia of Cancer

R. I. A. BELS, KAY M. LARHOLT, KENNETH D. KRANTZ, EDWARD C. BRYANT

The R.W. Johnson Pharmaceutical Research Institute, Raritan, New Jersey, USA

Key Words. Anemia · Cancer · Erythropoietin

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 rHuEPO 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 rHuEPO (100 U/kg) or placebo s.c. three times a week for up to eight weeks. In the two types of chemotherapy trials, patients were treated with rHuEPO (150 U/kg) or placebo SC three times a week 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 rHuEPO had a significantly greater ($p < .004$) increase in hematocrit than placebo-treated patients. In the two types of chemotherapy trials combined, utilizing an rHuEPO dose of 150 U/kg, rHuEPO-treated patients had significantly lower ($p \leq .009$) transfusion requirements (percentage of patients transfused and mean units of blood transfused per patient) than placebo-treated patients during months two and three, but not during month one. Quality-of-life parameters measured on a 100 mm visual analog scale significantly improved ($p < .05$) in rHuEPO-treated patients whose hematocrit increased $\geq 6$ percentage points, compared to corresponding quality-of-life changes in placebo-treated patients. rHuEPO was well tolerated compared to placebo.

The above results suggest that rHuEPO may be a useful agent to palliate the morbid consequences of the anemia that is often found in association with advanced cancer. The Oncologist 1996;1:140-150

INTRODUCTION

Advanced cancer is frequently associated with anemia which can significantly contribute to overall morbidity in these patients. The anemia found in 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 reticulocyteosis, 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 interleukin 1 (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 rHuEPO, rHuEPO may be a rational therapy for anemia in cancer patients. This paper will describe the effect of rHuEPO 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 Eastern Cooperative Oncology Group (ECOG) Scale; life expectancy was to be at least three months; patients were to be clinically stable for at least one month prior to study participation and were required to be at least 18 years of age. In the two types of chemotherapy trials, the patients were to receive cyclic chemotherapy for up to five days every three to four weeks.

Required laboratory values included: hemoglobin/hematocrit (HCT) <10.5 g/dl or 32%, respectively, to document prestudy anemia; neutrophils >500 cells/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 seven 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 rHuEPO 150 U/kg or a comparable volume of placebo SC three times per week for eight weeks or until an HCT of 38%-40% was attained. Patients enrolled in the two types of chemotherapy trials were randomized to rHuEPO 150 U/kg or a comparable volume of placebo SC three times per week for 12 weeks or until an HCT of 38%-40% was attained, after which the dose of study medication was titrated to maintain the HCT within the target range. After completion of the double-blind phase of these studies, open-label therapy with rHuEPO was permitted, but this paper will describe only the results of double-blind therapy.

**Analytic Technique**

The major efficacy criteria pertained to the effects of study medication on HCT, transfusion requirements and quality of life. For the purpose of these studies, “correction of anemia” was defined as attainment of an HCT ≥38% unrelated to transfusion, and “response to therapy” was defined as an increase of HCT of at least six 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 rHuEPO-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 HCT, 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 α = 0.05 level.

rHuEPO 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 rHuEPO.
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 rHuEPO, and 200 patients were randomized to placebo. Two hundred and six patients randomized to rHuEPO 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 1 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 2 presents additional baseline characteristics for patients enrolled in these trials. During the baseline period (the two months prior to study participation for the no-chemotherapy trials and the three months prior to study participation for the two types of chemotherapy trials), 45% of the rHuEPO-treated patients and 48% of the 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 rHuEPO group and 0.73 in the placebo group. The mean HCT immediately prior to study participation was 29.1% in rHuEPO-treated patients and 28.5% in the placebo-treated patients. These baseline HCTs were 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 HCT. Approximately 75% of the patients had endogenous serum EPO levels ≤150 mU/ml, and fewer than 5% of the 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 lower (p < .05) than in the no-chemotherapy and no-cisplatin chemotherapy populations.

### Table 1. Demographics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>rHuEPO (# = 213)</th>
<th>Placebo (# = 200)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>102</td>
<td>95</td>
</tr>
<tr>
<td>Female</td>
<td>111</td>
<td>105</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>179</td>
<td>172</td>
</tr>
<tr>
<td>Others</td>
<td>34</td>
<td>28</td>
</tr>
<tr>
<td>Age (years)</td>
<td>61.2</td>
<td>62.5</td>
</tr>
<tr>
<td>Height (inches)</td>
<td>66.5</td>
<td>66.2</td>
</tr>
</tbody>
</table>

### Table 2. Baseline characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>rHuEPO</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage transfused</td>
<td>44.7</td>
<td>48.4</td>
</tr>
<tr>
<td>Mean units transfused/patient/month</td>
<td>0.67</td>
<td>0.73</td>
</tr>
<tr>
<td>Mean HCT (%)</td>
<td>29.1</td>
<td>28.5</td>
</tr>
<tr>
<td>Mean neutrophil count (cells/µl)</td>
<td>4,163</td>
<td>4,017</td>
</tr>
<tr>
<td>Endo serum EPO level mU/ml</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>146</td>
<td>149</td>
</tr>
<tr>
<td>Median</td>
<td>76</td>
<td>85</td>
</tr>
<tr>
<td>Mean overall quality of life</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(mm on a 100 mm scale)</td>
<td>50.0</td>
<td>50.4</td>
</tr>
</tbody>
</table>

Figure 1. Distribution of baseline endogenous serum EPO levels pooled across all trials. Baseline serum EPO levels available for 348 patients.
Table 3 gives the histologic origin of tumors for patients randomized to rHuEPO and placebo. As is evident, patients participating in these trials had a wide variety of different tumor types. However, the distribution of tumor types was relatively similar in patients randomized to rHuEPO and placebo. Overall, approximately 32% of the patients had hematologic tumors (e.g., lymphoma, multiple myeloma or chronic lymphocytic leukemia), and approximately 69% of the patients had solid tumors, the distribution of which is given in Table 3.

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

Table 3. Distribution of tumor types

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>%</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>rHuEPO</td>
<td>Placebo</td>
</tr>
<tr>
<td>Hematologic</td>
<td>32.0</td>
<td>32.1</td>
</tr>
<tr>
<td>Non-Hematologic</td>
<td>68.0</td>
<td>67.9</td>
</tr>
<tr>
<td>Breast</td>
<td>11.2</td>
<td>9.0</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>10.7</td>
<td>12.6</td>
</tr>
<tr>
<td>Lung, non-small cell</td>
<td>10.2</td>
<td>9.0</td>
</tr>
<tr>
<td>Gynecologic</td>
<td>9.2</td>
<td>12.1</td>
</tr>
<tr>
<td>Lung, small cell</td>
<td>3.9</td>
<td>7.9</td>
</tr>
<tr>
<td>Head and neck</td>
<td>2.4</td>
<td>1.6</td>
</tr>
<tr>
<td>Esophagus</td>
<td>1.0</td>
<td>1.6</td>
</tr>
<tr>
<td>Unknown primary site</td>
<td>3.4</td>
<td>1.1</td>
</tr>
<tr>
<td>Others</td>
<td>5.8</td>
<td>7.9</td>
</tr>
</tbody>
</table>

Figure 2. Mean weekly HCT ± SE in rHuEPO- and placebo-treated patients in no-chemotherapy trials. $\triangle = \text{rHuEPO (100 U/kg); } \bigcirc = \text{placebo.}$
Interestingly, the largest transfusion requirements were found in cisplatin-treated patients (Table 7).

Since there is a discrete lag phase before the effect of rHuEPO becomes evident on erythropoiesis, it was hypothesized that rHuEPO 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 8 gives linear model transfusion requirements in the two types of chemotherapy trials stratified by months on therapy, month one versus months two and three combined. As is evident from Table 8, transfusion requirements were similar in rHuEPO and placebo-treated patients during month one, but transfusion requirements were substantially lower in rHuEPO-treated patients than in placebo-treated patients during months two and three. When the data from the chemotherapy trials were combined, transfusion requirements were significantly lower ($p < .009$) in rHuEPO-treated patients than in placebo-treated patients during months two and three, supporting the conclusion that rHuEPO in a dose of 150 U/kg three times a 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 rHuEPO-treated patients after the first month of therapy in this patient population may have been related to the relatively low dose of rHuEPO employed (100 U/kg) and the relatively short duration of follow-up (eight weeks), compared to the chemotherapy trials (using an rHuEPO 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 rHuEPO- and placebo-treated patients pooled across all study types. Quality-of-life scores improved in rHuEPO-treated patients from prestudy to post-study compared to 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 rHuEPO-treated responders (i.e., in patients whose HCT increased $\geq 6$ percentage points unrelated to transfusion) and placebo-treated patients. In contrast to the rHuEPO-treated population as a whole, the changes in quality-of-life scores in rHuEPO-treated responders were significantly greater ($p < .05$) than the corresponding changes in placebo-treated patients. Moreover, quality-of-life scores in rHuEPO-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 rHuEPO-treated cancer patients whose HCT increases significantly (e.g., $\geq 6$ percentage points) during the course of therapy.

Effect of Tumor Type and Tumor Infiltration of the Bone Marrow on Response to rHuEPO Therapy

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

Twenty-eight percent of rHuEPO-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 rHuEPO-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 rHuEPO-treated population taken as a whole and in the rHuEPO-treated responder population suggests that patients with tumor infiltration of the bone marrow respond to rHuEPO 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 rHuEPO therapy (change in HCT from baseline to final value) varied inversely with the baseline endogenous EPO level (Fig. 7). The HCT response to rHuEPO therapy was significantly greater than the HCT 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 HCT response to rHuEPO therapy and baseline endogenous serum EPO levels.

Transfusion Trigger and Intensity of Chemotherapy

In order to ensure that the HCT results reported above were not related to differential transfusion practice in rHuEPO- and placebo-treated patients, the HCT at the time of transfusion.

| Table 4. Change in HCT from baseline to last value |
| Treatment | # | Baseline Value (%) | Final Value (%) | Percentage Point Change |
| No Chemotherapy | rHuEPO | 63 | 29.3 | 32.1 | 2.8* |
| | Placebo | 55 | 27.6 | 27.5 | -0.1 |
| Chemotherapy | rHuEPO | 79 | 28.6 | 35.5 | 6.9* |
| | Placebo | 74 | 29.4 | 30.5 | 1.1 |
| Cisplatin | rHuEPO | 64 | 29.4 | 35.4 | 6.0* |
| | Placebo | 61 | 28.4 | 29.7 | 1.3 |

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

| Table 5. Correction of anemia/response to therapy unrelated to transfusion |
| Study Type/ Treatment Group | # | Correctors (HCT >38%) | Responders (HCT Increase >6%) |
| No Chemotherapy | rHuEPO | 63 | 20.6* | 31.7* |
| | Placebo | 55 | 3.6 | 10.9 |
| Chemotherapy | rHuEPO | 79 | 40.5* | 58.2* |
| | Placebo | 74 | 4.1 | 13.5 |
| Cisplatin | rHuEPO | 64 | 35.9* | 48.4* |
| | Placebo | 61 | 1.6 | 6.6 |

*Significantly greater (p < 0.008) than placebo response.

| Table 6. Change in HCT from baseline to final value in various tumor types |
| Tumor Types | # | rHuEPO | Placebo |
| | Baseline HCT(%) | Change in HCT(%) | Baseline HCT(%) | Change in HCT(%) |
| CLL | 7 | 29.5 | 6.0* | 29.7 | 0.9 |
| Myeloma | 19 | 29.8 | 3.7* | 28.7 | 0.3 |
| Lymphoma | 40 | 29.5 | 6.0* | 29.5 | 0.5 |
| Breast cancer | 22 | 28.4 | 6.5* | 29.3 | 1.6 |
| Lung cancer* | 29 | 29.2 | 6.4* | 28.6 | 1.1 |
| Prostate cancer | 23 | 28.3 | 2.3 | 27.2 | 0.1 |
| GI cancer | 21 | 28.2 | 5.8* | 28.3 | 1.6 |
| Gynecologic cancer | 18 | 28.8 | 7.7* | 28.0 | -0.3 |

*aSmall cell and non-small cell combined.

*p-value = 0.0776 for difference between r-huEPO and placebo.

*p-value = 0.0581 for difference between rHuEPO and placebo.

*Statistically significant (p ≤ 0.05) difference between rHuEPO and placebo.
transfusion in rHuEPO- and placebo-treated patients was determined. In each of the study types, the mean HCT at the
time of transfusion in rHuEPO- 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 rHuEPO- and placebo-treated groups.

The intensity of chemotherapy in the rHuEPO-treated
and placebo-treated patients in the two types of chemother-
apy trials was also compared to ensure that the reported
HCT responses were not related to differential intensity of
chemotherapy. Since patients in the two types of chemother-
apy studies received a wide variety of different chemothera-
pptic regimens, it was considered best to use a surrogate
marker for the intensity of chemotherapy. The most appro-
priate 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. The effect of
chemotherapy on platelet counts was also used as an addi-
tional 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 rHuEPO- and placebo-treated patients was compared.
The data presented in Table 9 suggest that the effect of
chemotherapy on neutrophil and platelet counts was similar
in rHuEPO- and placebo-treated patients; in addition, the
total dose of cisplatin administered to rHuEPO-treated and
placebo-treated patients was similar. Taken together, these
data suggest that rHuEPO- 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.

**Safety**

rHuEPO appeared to be tolerated well compared to
placebo in these trials. Seventy-four percent of rHuEPO-
treated patients completed double-blind therapy compared to
73% of placebo-treated patients. Seventeen percent of
rHuEPO-treated patients discontinued double-blind therapy
due to an adverse experience, death or disease progression
versus 14% of placebo-treated patients who discontinued
double-blind therapy for these reasons. Fifteen percent of

---

**Table 7.** Transfusion requirements in rHuEPO- and placebo-treated patients over entire course of trials

<table>
<thead>
<tr>
<th>Population</th>
<th>Proportion of Patients Transfused (%)</th>
<th>Mean Units of Blood Transfused Per Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Chemotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rHuEPO</td>
<td>63</td>
<td>33.3</td>
</tr>
<tr>
<td>Placebo</td>
<td>55</td>
<td>38.2</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rHuEPO</td>
<td>79</td>
<td>40.5</td>
</tr>
<tr>
<td>Placebo</td>
<td>74</td>
<td>48.6</td>
</tr>
<tr>
<td>Cisplatin Chemotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rHuEPO</td>
<td>64</td>
<td>53.1</td>
</tr>
<tr>
<td>Placebo</td>
<td>61</td>
<td>68.9</td>
</tr>
</tbody>
</table>

---

**Table 8.** Transfusion requirements in chemotherapy trials by months on study

<table>
<thead>
<tr>
<th>Population</th>
<th>Month 1</th>
<th>Months 2 and 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>#</td>
<td>% Transfused a</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rHuEPO</td>
<td>79</td>
<td>25.3</td>
</tr>
<tr>
<td>Placebo</td>
<td>74</td>
<td>27.0</td>
</tr>
</tbody>
</table>

(p = .056)

| Cisplatin               |         |                 |                        |         |                 |                        |
| rHuEPO                   | 64      | 43.8            | 1.71                   | 56      | 26.8            | 1.20                   |
| Placebo                  | 61      | 44.3            | 1.20                   | 55      | 56.4            | 2.00                   |

(p < .005) (p = .089)

| Chemotherapy & Cisplatin combined |         |                 |                        |         |                 |                        |
| rHuEPO               | 143     | 33.6            | 1.09                   | 126     | 27.8            | 1.04                   |
| Placebo              | 135     | 34.8            | 0.98                   | 123     | 45.5            | 1.81                   |

(p < .005) (p = .009)

aComparison with placebo performed by Fisher’s Exact Test.
bComparison with placebo performed by t-test.
rHuEPO-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 rHuEPO- and placebo-treated patients (data not shown). Taken together, these data would suggest that rHuEPO did not adversely affect outcome in the treated population.

Hypertension was noted as an adverse experience in 5.2% of rHuEPO-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 HCT in response to rHuEPO therapy. Seizures were noted in five (2.4%) rHuEPO-treated patients and in four (2%) placebo-treated patients. Seizures in two of the rHuEPO-treated patients occurred in the context of a significant increase in HCT 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 rHuEPO-treated patients and in 5.5% of placebo-treated patients.

Table 10 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 rHuEPO developed during the course of therapy. Variations in clinical laboratory parameters were similar in rHuEPO- 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 HCTs 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. They 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 rHuEPO can increase HCT and correct anemia in all three patient populations studied in short-term trials lasting up to 12 weeks. Responsiveness to rHuEPO 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 rHuEPO was administered in a dose of 150 U/kg three 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 rHuEPO-treated patients who had a substantial HCT response to therapy compared to 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 HCT response to rHuEPO therapy [7, 11].

Response to rHuEPO 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 [12]. However, there was no significant relationship between the response to rHuEPO 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 [13–15]. Consequently, it is possible that failure to find a significant relationship between baseline endogenous serum EPO levels and response to rHuEPO therapy may have been due to fluctuation of prestudy serum EPO levels related to prior cycles of chemotherapy, but this is speculative. The HCT response to rHuEPO therapy did not appear to be related to differential transfusion practice in rHuEPO-treated and placebo-treated patients. In addition, it appeared that rHuEPO- and placebo-treated patients received chemotherapy regimens of comparable myelosuppressive intensity based on similar effects on the neutrophil and platelet counts in the rHuEPO- and placebo-treated populations. Moreover, in the cisplatin trials, equivalent total doses of cisplatin were administered to rHuEPO- and placebo-treated patients. Consequently, it

Table 9. Intensity of chemotherapy (patients evaluable for efficacy in the chemotherapy and cisplatin studies)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Chemotherapy</th>
<th>Placebo</th>
<th>Chemotherapy</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>rHuEPO (# = 79)</td>
<td>Placebo (# = 74)</td>
<td>rHuEPO (# = 64)</td>
<td>Placebo (# = 61)</td>
</tr>
<tr>
<td>AUC (cells × wk/µl)</td>
<td>30,203</td>
<td>34,189</td>
<td>33,289</td>
<td>33,453</td>
</tr>
<tr>
<td>Number (%) of patients with ANC &lt;1,000 cells/µl</td>
<td>51 (64.6)</td>
<td>48 (64.9)</td>
<td>53 (82.8)</td>
<td>47 (77.0)</td>
</tr>
<tr>
<td>Number (%) of patients with ANC &lt;500/µl</td>
<td>32 (40.5)</td>
<td>23 (31.1)</td>
<td>38 (59.4)</td>
<td>30 (49.2)</td>
</tr>
<tr>
<td>Platelets/µl-change from baseline to final value × 10^9</td>
<td>−39.0</td>
<td>−48.0</td>
<td>−101.2</td>
<td>−97.3</td>
</tr>
<tr>
<td>Number (%) of patients with platelets &lt;50,000/µl</td>
<td>18 (22.8)</td>
<td>17 (23.0)</td>
<td>23 (35.9)</td>
<td>21 (34.4)</td>
</tr>
<tr>
<td>Number (%) of patients with platelets &lt;20,000/µl</td>
<td>2 (2.5)</td>
<td>2 (2.7)</td>
<td>7 (10.9)</td>
<td>4 (6.6)</td>
</tr>
<tr>
<td>Total Cisplatin dose (mg)</td>
<td>—</td>
<td>—</td>
<td>272.9</td>
<td>294.4</td>
</tr>
</tbody>
</table>

*aArea under the curve.

*bArea under the neutrophil time curve.

No statistically significant (p > .05) differences between rHuEPO response and corresponding placebo response.
is unlikely that the results described herein were related to
differential intensity of chemotherapy in the rHuEPO- and
placebo-treated populations.

rHuEPO was tolerated well in these trials. Based on a
similar percentage of patients in the rHuEPO 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 the percentage of patients who
died within 30 days of study completion in the rHuEPO
and placebo groups, rHuEPO did not appear to have a
deleterious effect on outcome in the treated population.

Although the risk of hypertension in rHuEPO-treated
cancer patients appears to be lower than in chronic renal
failure patients, hypertension may occasionally occur in
rHuEPO-treated cancer patients as the HCT rises signifi-
cantly above baseline values. This may be related to the
generally advanced age of these patients or to the pres-
ence of recognized or unrecognized underlying cardiore-
nal disease.

In summary, rHuEPO therapy increased HCT and cor-
rected anemia in cancer patients receiving no chemother-
apy, 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 three
times per week, transfusion requirements were lower
in rHuEPO-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
rHuEPO-treated patients who had a significant HCT
response to therapy, compared to the corresponding
responses in placebo-treated patients. rHuEPO was gener-
ally well tolerated compared to placebo. Based on the above,
rHuEPO may be a useful therapy to palliate the significant
anemia which may be related to advanced cancer or its ther-
apy when other causes of anemia (such as iron deficiency)
have been excluded.

**Acknowledgments**

The authors would like to thank the following principal
investigators for their valuable input and for enrolling their
patients into these trials:

- Norwood Anderson, MD
- Frank Andrews, MD
- John Bennett, MD
- Nirmala Bhoopalam, MD
- Douglas Blayney, MD
- Burke Brooks, MD
- Ronald Bukowski, MD
- Robert Carey, MD
- Delvyn Case, MD
- Ronald DeConti, MD
- Drue Denton, MD
- Rajendra Desai, MD
- Marc Ernstoff, MD
- Elliloth Fishkin, MD
- David Henry, MD
- Meyer Heyman, MD
- James Holland, MD
- Robert Jacobson, MD
- Stephen Jones, MD
- Alan Keller, MD
- John Kugler, MD
- Gary Lyman, MD
- Robert McMillan, MD
- John Merrill, MD
- Abraham Mittleman, MD
- Joseph Moore, MD
- John Neefe, MD
- Craig Nichols, MD
- James Neidhart, MD
- David Oblon, MD
- John Rainey, MD
- John Ruckdeschel, MD
- Sydney Salmon, MD
- Richard Silver, MD
- Milan Slavik, MD
- Richard Smalley, MD
- Anna Marie Storniolo, MD
- Gary Tansino, MD
- Mary Todd, MD
- Galen Wampler, MD
- Richard Wheeler, MD
- Ralph Zalusky, MD
- Paul Zorsky, MD

Reprinted from *Blood Cell Growth Factors: Their Present
and Future Use in Hematology and Oncology, Beijing
REFERENCES

7 Data on file. R. W. Johnson Pharmaceutical Research Institute, Raritan, NJ, USA.