SYNOPSIS

A Double–Blind, Placebo–Controlled Study With Open–Label Follow–Up to Determine the Safety and Efficacy of r-HuEPO, Administered Subcutaneously, in Chronic Anemia Induced by Advanced Cancer (Protocols H87–032, 87–014, 87–015)[1]

STUDY DATES: 11/87 – 06/90

INVESTIGATORS:

Frank Andrews, MD, VA Medical Center, Seattle, WA 98108
John Bennett, MD, University of Rochester Medical Center, Rochester, NY 14642
Nirmala Bhoopalam, MD, Edward J. Hines VA Hospital, Hines, IL 60141
Burke Brooks, Jr., MD, Ochsner Clinic of Baton Rouge, Baton Rouge, LA 70816
Robert Carey, MD, Massachusetts General Hospital, Boston, MA 02114
Delvyn Case, MD, Maine Center for Cancer Medicine, Portland, ME 04120
Drue Denton, MD, Barrett Center for Cancer Prevention, Research and Treatment, Cincinnati, OH 45267–0501
Marc Ernstoff, MD, University of Pittsburgh School of Medicine, Pittsburgh, PA 15201
Ellioth Fishkin, MD, Elizabeth General Medical Center, Elizabeth, NJ 07201
David Henry, MD, Graduate Hospital, Philadelphia, PA 19146
Meyer Heyman, MD, The University of Maryland Cancer Center, Baltimore, MD 21201
Robert Jacobson, M.B., Georgetown University Hospital, Washington, DC 20007
Stephen Jones, MD, Sammons Cancer Center, Dallas, TX 75246
John Kugler, MD, Oncology – Hematology Associates of Central Illinois, Peoria, IL 61603
Gary Lyman, MD, H. Lee Moffitt Cancer Center, Tampa, FL 33612
Abraham Mittleman, MD, New York Medical College, Valhalla, NY 10595
Joseph Moore, MD, Duke University Hospital, Durham, NC 27710
John R. Neefe, MD, University of Kentucky, Lexington, KY 50436
Craig R. Nichols, MD, University Hospital A109, Indianapolis, IN 46223
David Oblon, MD, University of Florida Medical College, Gainesville, FL 32610
Richard Silver, MD, New York Hospital, New York, NY 10021
Anna Maria Storniolo, MD, University of California, San Diego, CA 92103
Mary Todd, MD, Yale University School of Medicine, New Haven, CT 06510
Galen Wampler, MD, Medical College of Virginia, Richmond, VA 23298
Richard H. Wheeler, MD, University of Alabama at Birmingham, Birmingham, AL 35294
Ralph Zalusky, MD, Beth Israel Hospital, New York, NY 10003
Paul Zorsky, MD, George Washington University Medical Center, Washington, DC 20037

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[1] The design of the three protocols was essentially identical. Based on this, the results from the three protocols have been combined for this report. In general, responses to r–HuEPO relative to placebo in the combined protocols were similar to responses in each protocol alone. Data are presented by individual protocol in the data presentations in the APPENDICES.

STUDY DESIGN: This was a multicenter, double–blind, placebo–controlled, parallel group, randomized study of the safety and efficacy of subcutaneous administration of r–HuEPO in the treatment of anemia secondary to advanced cancer. A total of 124 patients were enrolled in the three virtually identical protocols and randomly assigned to one of two treatment groups; one group (65 patients) received r–HuEPO 100 U/kg and the other group (59 patients) received a comparable volume of placebo subcutaneously (s.c.) three–times–a–week for up to eight weeks. Patients who achieved an hematocrit level of 38–40% or whose hematocrit dropped by ≥ 15% from baseline (e.g., from 30%–25.5%) by Week 4 of double-blind therapy were allowed to move to the open–label phase of the study during which time all patients received r–HuEPO at a dose titrated to maintain an hematocrit level of between 38–40%. This report discusses the results from the double–blind phase of the study.

The primary determination of r–HuEPO efficacy was based on the effect of study medication on transfusion requirements (cumulative number of units of blood transfused, proportion of patients transfused) and hematocrit (mean change from baseline to final value, number of patients who achieved the target hematocrit of 38% unrelated to transfusion [Correctors], number of patients who experienced an increase in hematocrit of ≥ six percentage points from baseline unrelated to transfusion [Responders]). The secondary determination of r–HuEPO efficacy was based on the following evaluations: the patient's Quality of Life Assessment (change from pre– to post–study) and the Physicians' Global Evaluation of Study Medication. Of the primary and secondary analyses described above, changes in erythroid variables and Quality of Life measures were planned analyses as stated in the study protocols. Additional analyses that were performed after a review of the actual data included: 1) transfusion results (cumulative and by–month); and 2) survival analysis.

Safety evaluations were made on the basis of the incidence and severity of any adverse or unusual experiences reported during double-blind therapy, incidence of death, clinical laboratory tests, r–HuEPO antibody titers, vital sign measurements, and patient discontinuation information. In addition, a complete physical examination and 12-lead ECG were performed prior drug administration and after completion of double-blind dosing.

PATIENT POPULATION: A total of 124 patients were enrolled in the three protocols summarized in this report. Of these patients, 65 patients received r–HuEPO and 59 patients received placebo. Six patients (two r–HuEPO, four placebo) were on therapy less than 15 days and were not included in the primary analyses of patients evaluable for efficacy. All patients were included in a supportive intent-to-treat analysis of efficacy and all patients were included in analyses of safety. There was a significant between–group difference in the mean age of the patients enrolled in the study (62.1 years, r–HuEPO; 67.2 years, placebo; $p = 0.028$). In addition, among the patients evaluated for efficacy, a higher percentage of placebo patients than r–HuEPO patients exhibited a primary hematologic cancer type at baseline (41.8%, placebo; 25.4%, r–HuEPO; $p = 0.078$). There was also a significant difference between treatment groups in the mean baseline hematocrit level (29.3%, r–HuEPO; 27.6%, placebo; $p = 0.018$). Of the 124 patients evaluated for safety, 36 patients (18 in each treatment group) discontinued double–blind therapy prematurely: 14 for therapy failure, 11 for adverse experiences, five for disease progression, three for death, two for protocol violation, and one for other reasons.

RESULTS

EFFICACY

With regard to the primary evaluation of efficacy, the cumulative 2-month transfusion rate on–study remained relatively constant in r–HuEPO treated patients and increased in placebo–treated patients over the course of double–blind therapy. The efficacy of r-HuEPO was also supported by clinically and statistically significant improvement in comparison to placebo–treated patients in the following evaluations: increase in hematocrit, achievement of the target hematocrit (38%) unrelated to transfusion, increase in hematocrit of ≥ six percentage points unrelated to transfusion, and a favorable Physicians' Global Evaluation of study medication.

Transfusion Requirements. r–HuEPO treatment had no significant effect on the cumulative 2–month transfusion rate compared with placebo treatment. The mean transfusion rate in r–HuEPO–treated patients was 1.49 units/patient/2 months at baseline and 1.52 units/patient/2 months on study. The mean transfusion rate in placebo–treated patients was 1.69 units/patient/2 months at baseline and 2.19 units/patient/2 months on study. A total of 33.3% of r–HuEPO–treated patients and 38.2% of placebo–treated patients required transfusions during the study. From the results of a linear model analysis that adjusted for the imbalance in baseline hematocrit (r–HuEPO, 29.3%; placebo, 27.6%; $p = 0.018$) transfusion requirements were not found to be substantially different between treatment groups (r–HuEPO, 1.95 units/patient/2 months; placebo, 2.68 units/patients/2 months). The lack of significant treatment group differences in the transfusion data may be the result of the short duration of treatment (two months).

Hematocrit. Hematocrit levels increased throughout the study in the r–HuEPO group, from a baseline mean of 29.3% to a final mean value of 32.1%; in contrast, hematocrit levels remained stable throughout the course of treatment for placebo–treated patients (baseline mean 27.6%, final mean 27.5%). The between group difference in mean change from baseline to final hematocrit value was significantly higher among r–HuEPO–treated patients than placebo–treated patients. The r–HuEPO–treated patients experienced a 2.9 percentage point greater mean change from baseline to final hematocrit compared to placebo–treated patients. In addition to the analysis of simple mean hematocrits, linear model analyses were conducted that adjusted estimates of hematocrit response to r–HuEPO therapy for effects of covariables such as baseline hematocrit and endogenous EPO levels. The linear model estimate of hematocrit differences between treatment groups showed that r–HuEPO-treated patients experienced a 2.5 percentage point significantly greater change from baseline to final value compared to placebo–treated patients at the average value of endogenous EPO. Patients with lower endogenous EPO values at baseline were estimated to have a greater hematocrit response to r–HuEPO than patients with higher EPO values. A significantly superior hematocrit response for r–HuEPO–treated patients compared to placebo was found for all baseline endogenous EPO levels ≤ 174 mU/mL. At the 174 mU/mL EPO level, the linear model estimate of hematocrit response to r–HuEPO was a 2.8 percentage point greater change from baseline to final value compared to placebo. A summary of the changes in the simple mean hematocrit is presented in the following TABLE.

Mean Change in Baseline to Final Value for Hematocrit
(Patients Evaluated for Efficacy in the Non-chemotherapy Study)

Parameter	Hematocrit (%) Mean ± Std. Dev. r-HuEPO (N = 63)	Placebo (N = 55)
Baseline[a]	29.3 ± 4.0	27.6 ± 3.9
Final Value[b]	32.1 ± 6.8	27.5 ± 4.0
Change from Baseline[c]	2.8 ± 6.3	-0.1 ± 4.0

[a]Significant between-group difference ($p = 0.0181$).
[b]Significant between-group difference ($p < 0.0001$).
[c]Significant between-group difference ($p = 0.0045$).

An intent-to-treat analysis of hematocrit levels was also performed for all patients including the six patients whose time on-study was less than 15 days. The results of the intent-to-treat analysis were comparable to these of the primary efficacy analysis.

Response to therapy/Correction of anemia. Thirteen (20.6%) of the r–HuEPO–treated patients versus two (3.6%) of the placebo–treated patients ($p = 0.006$) reached the target hematocrit of 38% unrelated to transfusion (Correctors). There were 20 (31.7%) patients in the r–HuEPO–treatment group who responded to therapy with a ≥ six percentage point increase in hematocrit from baseline unrelated to transfusion (Responders), versus six (10.9%) placebo–treated patients ($p = 0.008$).

Quality of Life Assessment

There were no statistically significant between–group differences in the change in any Quality–of–Life measurement evaluated from pre–study to post–study.

Physicians' Global Evaluation of Study Medication. The distribution of Physicians' Global Evaluation scores was significantly better for the r–HuEPO group versus placebo–treated patients ($p \leq 0.001$), with study medication given to 25 r–HuEPO–treated patients (41.0%) being rated as good, very good, or excellent versus seven placebo–treated patients (13.0%).

SAFETY

Adverse experiences. One hundred–eight (55 r–HuEPO, 53 placebo) patients reported at least one adverse experience during double–blind treatment. There were no significant differences between treatment groups in the overall percentage of patients for whom adverse experiences were reported during the study or in the patient incidence of any given adverse experience summarized by primary term. Adverse experiences that occurred in 10% or more of r–HuEPO–treated patients were: asthenia (r–HuEPO, 21.5%; placebo 11.9%), trunk pain (r–HuEPO, 15.4%; placebo 5.1%), nausea (r–HuEPO, 15.4%, placebo, 17.0%), fatigue (r–HuEPO, 12.3%; placebo, 18.6%), edema (r–HuEPO, 12.3%; placebo 6.8%) and constipation (r–HuEPO, 10.8%; placebo, 10.2%).

Three patients (all in the r–HuEPO treatment group) experienced hypertension or elevated blood pressure as an adverse experience during double–blind therapy. One other r–HuEPO–treated patient exhibited elevated blood pressure on–study, although the investigator did not list this event as an adverse experience for this patient. There were no statistically significant treatment group differences in the mean change from baseline to final value for systolic or diastolic blood pressure.

Discontinuations due to adverse experiences. Eleven patients (four r–HuEPO, seven placebo) discontinued treatment as a result of adverse experiences during the course of double–blind therapy. The investigators did not consider the adverse experiences of eight of these patients as being drug–related. The investigators considered the adverse experiences of placebo–treated patients #207 (ventricular tachycardia) and #41526 (nausea and vomiting) as possibly related to the study medication. The investigator could not determine whether the adverse experience exhibited by r–HuEPO–treated patient #7044 (asthenia) was related to therapy. Eleven (16.9%) r-HuEPO-treated patients discontinued study medication due to death, disease progression, or adverse experiences versus eight (13.6%) in the placebo group.

Deaths. Twenty-six patients (13 r–HuEPO, 13 placebo) died during or within 30 days following discontinuation or completion of double–blind therapy. None of these deaths were regarded by the investigators as study drug–related. The survival curve of the patients who received r-HuEPO was very similar to the survival curve of the patients who received placebo during the double-blind phase of the study (p= 0.941).

Safety reports. There were four patients (all in the r–HuEPO treatment group) reporting adverse experiences during the double–blind phase of therapy that required filing of an IND Safety Report to the FDA (events: deep vein thrombosis, secondary tumor, cerebrovascular accident, and acute renal failure).

Antibody titers. None of the 72 patients (36 r–HuEPO, 36 placebo) who had antibody titers measured both pretherapy and following completion of double–blind therapy exhibited a positive titer for anti-r–HuEPO antibodies. Likewise, none of the 42 patients (23 r–HuEPO, 19 placebo) who had either a pre–study or post–study determination exhibited a positive antibody titer against r–HuEPO.

CONCLUSIONS

The results of this double–blind, placebo–controlled study demonstrate that r–HuEPO administered subcutaneously at a dose of 100 U/kg, three–times–a–week can significantly and safely increase hematocrit in anemic cancer patients not undergoing chemotherapy.

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