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TITLE: A Double-Blind, Placebo-Controlled Study to Determine the Safety and Efficacy of r-HuEPO, Administered Subcutaneously, in Patients With Anemia Secondary to Advanced Cancer and Aggressive Cyclic Chemotherapy

PROTOCOLS: I88-037, 87-016, 87-017

INVESTIGATORS:

Norwood Anderson, M.D., The Cancer Center, Boston, MA 02120
Frank Andrews, M.D., VA Medical Center, Seattle, WA 98108
John Bennett, M.D., University of Rochester Medical Center, Rochester, NY 14642
Douglas Blayney, M.D., Wilshire Oncology Medical Group, Glendora, CA 91740
Burke Brooks, M.D., Ochsner Clinic of Baton Rouge, Baton Rouge, LA 70816
Ronald Bukowski, M.D., Cleveland Clinic/Cancer Center, Cleveland, OH 44106
Robert Carey, M.D., Massachusetts General Hospital, Boston, MA 02114
Delvyn Case, M.D., Maine Center for Cancer Medicine, Portland, ME 04120
Bruce W. Dana, M.D., Oregon Health Sciences University, Portland, OR 97201
Ronald DeConti, M.D., Albany Veterans Administration Center, Albany, NY 12208
Drue Denton, M.D., Barrett Center for Cancer Prevention, Research and Treatment, Cincinnati, OH 45267-0501
Marc Ernstoff, M.D., University of Pittsburgh School of Medicine, Pittsburgh, PA 15201
Ellioth Fishkin, M.D., Elizabeth General Medical Center, Elizabeth, NJ 07201
David Henry, M.D., Graduate Hospital, Philadelphia, PA 19146
Meyer Heyman, M.D., The University of Maryland Cancer Center, Baltimore, MD 21201
James Holland, M.D., Mt. Sinai Medical Center, New York, NY 10029
Robert Jacobson, M.D., Georgetown University Hospital, Washington, DC 20007
Stephen E. Jones, M.D., Sammons Cancer Center, Dallas, TX 75246
Alan M. Keller, M.D., Cancer Care Associates, Tulsa, OK 74136
John Kugler, M.D., Oncology - Hematology Associates of Central Illinois, Peoria, IL 61603
Gary Lyman, M.D., H. Lee Moffitt Cancer Center, Tampa, FL 33612
Robert McMillan, M.D., Scripps Clinic and Research Foundation, La Jolla, CA 92037
John Merrill, M.D., Hematology Oncology Associates, Chicago, IL 60611
Joseph Moore, M.D., Duke University Hospital, Durham, NC 27710
John R. Neefe, M.D., University of Kentucky, College of Medicine, Lexington, KY 40536
Craig R. Nichols, M.D., University Hospital, Indianapolis, IN 46223
David Oblon, M.D., University of Florida Medical College, Gainesville, FL 32610
John Rainey, M.D., Lafayette, LA 70503
Sydney E. Salmon, M.D., The University of Arizona, The Arizona Cander Center College of Medicine, Tucson, AZ 85724
Richard Silver, M.D., New York Hospital, Cornell Medical Center, New York, NY 10021
Milan Slavik, M.D., VA Medical Center, Wichita, KS 66103
Anna Maria Storniolo, M.D., University of California, San Diego, San Diego, CA 92103
Galen Wampler, M.D., Medical College of Virginia, Virginia Commonwealth University Richmond, VA 23298
Ralph Zalusky, M.D., Beth Israel Hospital, New York, NY 10003
Paul Zorsky, M.D., George Washington University Medical Center, Washington, DC 20037

STUDY DATES: 10/88 - 06/90

SYNOPSIS

A Double-Blind, Placebo-Controlled Study to Determine the Safety and Efficacy of r-HuEPO, Administered Subcutaneously,in Patients With Anemia Secondary to Advanced Cancer and Aggressive Cyclic Chemotherapy (Protocols I88-037, 87-016, 87-017)[1]

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Paul Zorsky, M.D., George Washington University Medical Center, Washington, DC 20037

STUDY DESIGN: These were multicenter, double-blind, parallel group, placebo-controlled, randomized studies of the safety and efficacy of subcutaneous administration of r-HuEPO in the treatment of anemia secondary to advanced cancer and aggressive cyclic chemotherapy. A total of 157 patients were enrolled in the three protocols and randomly assigned to one of two treatment groups; one group (81 patients) received r-HuEPO 150 U/kg and the other group (76 patients) received a comparable volume of placebo, subcutaneously (s.c.), three-times-a-week for 12 weeks. All patients completing the double-blind phase of the study were eligible to enter the open-label phase during which all patients received r-HuEPO at a dose titrated to maintain hematocrit between 38-40%. This report discusses the results from the double-blind phase of these studies.

1 The design of the three protocols (I88-037, 87-016, 87-017) was essentially identical, and analysis of the demographics and other data confirmed that the results could be pooled across protocols. Based on this and an agreement from the FDA (06/08/90 meeting with CBER), the results from the three studies have been combined for this report. By-patient data listings as well as data summaries are presented by individual protocol in the APPENDICES.

Determination of efficacy was based on the effect of the study medication on hematocrit (change from baseline to last value), number of patients who responded to therapy, the patient's Quality of Life Assessment (change from baseline to last value), the Physicians' Global Evaluation of Study Medication and transfusion requirements (cumulative number of units of blood transfused).

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

PATIENT POPULATION: A total of 157 patients were enrolled in the three studies summarized in this report. Of these patients, 81 received r-HuEPO and 76 received placebo. Four patients (two r-HuEPO, two placebo) were on therapy less than 15 days and therefore were not included in the determinations of efficacy. All patients were evaluable for safety. Thirty-one patients (18 r-HuEPO, 13 placebo) discontinued double-blind treatment prematurely. The frequencies of primary reason for discontinuation were as follows: adverse experiences (11), death (three), disease progression (seven), protocol violation (four), physician/sponsor decision (three) and personal reasons (three).

RESULTS

EFFICACY

Patients who were treated with r-HuEPO experienced significant ($p \leq 0.05$) improvement in comparison to placebo-treated patients in the following primary evaluations of efficacy: increase in hematocrit, achievement of the target hematocrit (38%) unrelated to transfusion, increase in hematocrit of ≥ six percentage points unrelated to a transfusion, favorable Physicians' Global Evaluation of Study Medication and improvement in Energy Level in those patients reaching a hematocrit of ≥ 38%. There was also a tendency toward a decreased cumulative transfusion rate on study for the r-HuEPO treatment group and an increased transfusion rate for the placebo group.

Hematocrit. The final hematocrit value and the change in baseline to final hematocrit in the r-HuEPO group were significantly ($p \leq 0.05$) greater than the corresponding values in the placebo group. Hematocrit levels rose throughout the study in the r-HuEPO group, increasing from a baseline mean of 28.6% to a final mean value of 35.4% (change of 6.9%); in contrast, hematocrit remained stable throughout the course of treatment for placebo-treated patients (baseline mean, 29.4%; final mean, 30.4%; change, 1.1%). r-HuEPO-treated patients experienced a 5.8% increase from baseline to final hematocrit above the change in placebo-treated patients. A summary of the changes in hematocrit is presented in the TABLE below.

Mean Change in Baseline to Last Value for Hematocrit
(Patients Evaluated for Efficacy in Protocols I88-037, 87-016, 87-017)

Parameter	Mean ± Std Dev	
	r-HuEPO (N = 79)	Placebo (N = 74)
Baseline	28.6 ± 3.9	29.4 ± 3.0
Last Value[a]	35.4 ± 6.0	30.4 ± 4.0
Change from Baseline[a]	6.9 ± 6.0	1.1 ± 4.3

[a] Significant ($p \leq 0.0001$) between-group difference.

Response to Therapy. Thirty-two (40.5%) of the r-HuEPO-treated patients versus three (4.1%) of placebo-treated patients reached the target hematocrit of ≥ 38% unrelated to transfusion (Correctors). This difference between treatment groups in the number of patients achieving the target hematocrit was statistically significant ($P \leq 0.05$). There were 46 (58.2%) r-HuEPO-treated patients who responded to therapy with greater than or equal to a six percentage point increase in hematocrit unrelated to transfusion (Responders), versus 10 (13.5%) of placebo-treated patients. This difference between treatment groups was also statistically significant ($p \leq 0.05$).

Quality of Life Assessment

All Patients. While there were no significant between-group differences in any quality of life assessments ($p > 0.05$), the results were more favorable for the r-HuEPO-treated patients in all categories. Patients in the r-HuEPO-treatment group reported a statistically significant ($p \leq 0.05$) post-study improvement in energy level and ability-to-perform daily activities when compared with pre-study assessments, and a tendency toward a pre- to post-study improvement in overall quality-of-life ($p = 0.083$). Patients in the placebo group experienced no statistically significant pre- to post-study improvements in either energy level, ability to perform daily activities, or in overall quality of life ($p > 0.05$).

Patients who responded to therapy. r-HuEPO-treated patients whose anemia was corrected experienced significant ($p \leq 0.05$) pre- to post-study improvement in energy level, ability to perform daily activities, and overall quality of life. There was a significant ($p \leq 0.05$) between-group difference (improvement favoring correctors) in the pre- to post-study energy level and a between-group difference ($p = 0.059$; improvement favoring correctors) in mean changes in overall quality of life when correctors receiving r-HuEPO were compared with placebo patients. Responders to r-HuEPO therapy had a significant ($p \leq 0.05$) pre- to post-study improvement in energy level and the ability to perform daily tasks, and a tendency toward improvement ($p = 0.076$) in overall quality of life.

Physicians' Global Evaluation of Study Medication. The distribution of scores for the Physicians' Global Evaluation of Study Medication was significantly ($p \leq 0.05$) better for r-HuEPO-treated patients versus placebo-treated patients, with study medication given to 44 (57.9%) of r-HuEPO-treated patients being rated as good, very good or excellent versus 24 (32.9%) for placebo-treated patients.

Transfusion Requirements. r-HuEPO treatment had no significant effect on transfusion rate compared with placebo treatment ($p > 0.05$). However, while transfusion requirements in r-HuEPO-treated patients appeared to be stabilized on-study (mean transfusion rate: baseline, 2.34 units/patient/three months; on-study, 2.03 units/patient/days on study), mean transfusion rates for placebo-treated patients increased from a baseline value of 2.11 units/patient/three months to an on-study value of 2.75 units/patient/days on study, the net result being that r-HuEPO-treated patients had a 26.2% lower transfusion rate on-study than placebo-treated patients. In the population as a whole, a smaller percentage of r-HuEPO-treated patients (40.5%) than placebo-treated patients (48.6%) required transfusions during the study ($p > 0.05$). While there were no differences in transfusion requirements during Month 1 of the study, the mean transfusion rate for r-HuEPO-treated patients was lower than that for placebo patients during Month 3 (r-HuEPO, 0.39 units/month/patient; placebo, 0.86 units/month/patient; $p = 0.073$) and during Months 2 and 3 combined (r-HuEPO, 0.91 units/2 months/patient; placebo, 1.65 units/2 months/patient; $p = 0.056$).

SAFETY

Adverse experiences. Seventy-three r-HuEPO-treated patients (90.1%) and 71 placebo-treated patients (93.4%) reported adverse experiences during double-blind therapy. There was no statistically significant difference between the groups in the overall percentage of patients for whom adverse experiences were reported during the study ($p > 0.05$). There was a statistically significant ($p \leq 0.05$) increase in the incidence of mild to moderate diaphoresis in r-HuEPO-treated patients (11.1%) compared with the placebo-treated patients (1.3%), but this adverse experience was not considered to be clinically significant. Adverse experiences which occurred in 10% or more of r-HuEPO-treated patients are as follows: pyrexia (r-HuEPO, 30.9%; placebo, 19.7%), nausea (r-HuEPO, 28.4%; placebo, 29.0%), diarrhea (r-HuEPO, 22.2%; placebo, 10.5%), fatigue (r-HuEPO, 17.3%; placebo, 21.1%), cough (r-HuEPO, 17.3%; placebo, 7.9%), dizziness (r-HuEPO, 16.1%; placebo, 7.9%), asthenia (r-HuEPO, 16.1%; placebo, 19.7%), edema (r-HuEPO, 16.1%; placebo, 7.9%), vomiting (r-HuEPO, 16.1%; placebo, 19.7%), upper respiratory infection (r-HuEPO, 12.4%; placebo, 7.9%), shortness of breath (r-HuEPO,

11.1%; placebo, 10.5%), skin reactions at the injection site (r-HuEPO, 11.1%; placebo, 15.8%) and diaphoresis (r-HuEPO, 11.1%; placebo, 1.3%).

Six patients (four r-HuEPO, two placebo) experienced hypertension or elevated blood pressure as an adverse experience during double-blind therapy. Individual case histories suggest that increasing hematocrit in cancer patients may pose some risk of hypertension, indicating that hematocrit and blood pressure should be carefully monitored in r-HuEPO-treated cancer patients.

Discontinuations due to adverse experiences. Eleven patients (nine r-HuEPO, two placebo) discontinued the double-blind treatment because of adverse experiences. Two of these patients (both r-HuEPO-treated) had adverse experiences that were characterized by the investigators as possibly related to the therapy (#404, seizures; #19125, nasal drip, watery eyes, shortness of breath, malaise). Thirteen (16.0%) r-HuEPO-treated patients discontinued study medication due to death, disease progression or adverse experiences versus eight (10.5%) in the placebo group.

Deaths. Ten patients (six r-HuEPO, four placebo) died during or shortly following discontinuation of double-blind therapy. None of these deaths were characterized by the investigators as being related to the study medication.

Safety reports. There were eight patients (five r-HuEPO, three placebo) who participated in these studies reporting adverse experiences during double-blind therapy that required filing of an IND Safety Report to the FDA.

Antibody titers. None of the 82 patients (38 r-HuEPO, 44 placebo) who had a pre- and on-study determination exhibited a positive titer for anti-r-HuEPO antibodies.

CONCLUSIONS

The results of this double-blind, placebo-controlled study demonstrate that r-HuEPO administered subcutaneously at a dose of 150 U/kg, three-times-a-week can significantly and safely increase hematocrit in anemic cancer patients treated with aggressive cyclic chemotherapy.

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