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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 Cisplatin Chemotherapy

PROTOCOLS: 188-036, 87-018, 87-019

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STUDY DATES: 10/88 - 7/90

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 Cisplatin Chemotherapy (Protocols 188-036, 87-018, 87-019)¹

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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 cancer and cyclic cisplatin-containing chemotherapy. A total of 132 patients were enrolled in the three protocols and randomly assigned to one of two treatment groups: one group (67 patients) received r-HuEPO 150 U/kg and the other group (65 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.

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 and the patient's Quality of Life Assessment (change from baseline to last value), the Physician's Global Evaluation of the Study Medication and transfusion requirements (number of units transfused per patient over the course of the study and the proportion of patients transfused on-study).

¹ The design of the three protocols (188-036, 87-018, 87-019) 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.

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 the study and drug administration and after completion of double-blind dosing.

PATIENT POPULATION: A total of 132 patients were enrolled in the three studies summarized in this report. Of these patients, 67 received r-HuEPO and 65 received placebo. Seven patients (three r-HuEPO, four placebo) were on therapy less than 15 days and therefore were not included in the determinations of efficacy. All patients are included in all analyses of safety. Forty-three patients (20 r-HuEPO, 23 placebo) discontinued double-blind treatment prematurely: 17 for adverse experiences, three for death, four for disease progression, four for protocol violation, eight for physician/sponsor decision, five for personal reasons, and two for other reasons.

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 ($\geq 38\%$) unrelated to transfusion, increase in hematocrit of \geq six percentage points unrelated to transfusion, improvement in overall quality of life and a more favorable distribution of scores for the Physicians' Global Evaluation of Study Medication. During Month 2 of the study, significantly ($p \leq 0.05$) fewer r-HuEPO-treated patients than placebo-treated patients required transfusions. In addition, a smaller percentage of r-HuEPO-treated patients than placebo-treated patients required transfusions during the three months of the study. There was also improvement in overall quality of life in those r-HuEPO-treated patients reaching a hematocrit of $\geq 38\%$, and improvement in energy level, ability to perform daily activities, and overall quality of life in those r-HuEPO-treated patients who responded to therapy with a \geq six percentage point increase in hematocrit.

Hematocrit. The endpoint hematocrit value and the change in baseline to endpoint hematocrit in 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 of 29.4% to a final mean value of 35.4% (change of six percentage points); in contrast, hematocrit remained stable throughout the course of treatment for placebo-treated patients (baseline mean, 28.4%; final mean, 29.7%; change, 1.3 percentage points). r-HuEPO-treated patients experienced a 4.7 percentage point increase from baseline to endpoint hematocrit above the change in placebo-treated patients. A summary of changes in hematocrit is presented in the following TABLE.

Mean Change in Baseline to Endpoint for Hematocrit
(Patients Evaluated for Efficacy in Protocols I88-036, 87-018, 87-019)

Parameter	Mean \pm Std. Dev.	
	r-HuEPO (N = 63)	Placebo (N = 61)
Baseline	29.4 \pm 4.0	28.4 \pm 4.5
Endpoint Value	35.4 \pm 7.0 ^a	29.7 \pm 4.5 ^a
Change from Baseline	6.0 \pm 7.0 ^a	1.3 \pm 5.0 ^a

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

Response to Therapy. Twenty-three (35.9%) of the r-HuEPO-treated patients versus one (1.6%) of the placebo-treated patients reached the target hematocrit of $\geq 38\%$ unrelated to transfusion (Correctors). This difference between treatment groups in the number of patients achieving the target hematocrit (Correctors) was statistically significant ($p \leq 0.05$). There were 31 (48.4%) 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 4 (6.6%) of placebo-treated patients. This difference between treatment groups was also statistically significant ($p \leq 0.05$).

Quality of Life Assessment Patients in the r-HuEPO-treated group reported a statistically significant ($p \leq 0.05$) post-study improvement in energy level, ability to perform daily activities, and overall quality of life when compared with pre-study assessments. The amount of change in overall quality of life for the r-HuEPO-treated group (12.9) was greater ($p = 0.013$) than that for the placebo-treated group (-0.9 points). Patients in the placebo group experienced a statistically significant ($p \leq 0.05$) improvement in energy level, but no improvement in ability to perform daily activities or in overall quality of life.

Physicians' Global Evaluation of Study Medication. The distribution of Physicians' Global Evaluation scores was significantly ($p \leq 0.05$) better for the r-HuEPO group versus placebo-treated patients, with 34 (57%) of r-HuEPO-treated patients being rated as good, very good, or excellent versus 15 (26%) for placebo-treated patients.

Transfusion Requirements. Compared with placebo treatment, r-HuEPO treatment had no significant ($P > 0.05$) effect on cumulative transfusion rate over the course of the three month therapy period. In the population as a whole, a smaller percentage of r-HuEPO-treated patients (53.1%) than placebo-treated patients (68.9%) required transfusions during the study. When transfusion requirements were examined during each study month, significantly fewer r-HuEPO-treated (21.4%) than placebo-treated patients (49.1%) required transfusions during Month 2 ($p \leq 0.05$), in contrast with Month 1 when the proportion of patients transfused was similar between the two groups (r-HuEPO, 43.8%; placebo, 44.3%; $p > 0.05$). There was also a tendency ($p = 0.057$) toward reducing the mean transfusion rate in r-HuEPO-treated patients (0.71 units/month/patient) compared with placebo (1.30 units/month/patient) during Month 2. Similar results were found for mean transfusion rate ($p = 0.089$) and the proportion of patients transfused on-study ($p \leq 0.05$) when data from Months 2 and 3 were analyzed together.

SAFETY

Adverse experiences. Fifty-eight r-HuEPO-treated (86.6%) and 58 placebo-treated patients (89.2%) reported adverse experiences during double-blind therapy. With the exception of shortness of breath which was significantly ($p \leq 0.05$) more prevalent in placebo-treated patients (20%) than in r-HuEPO-treated patients (7%), there were no statistically significant differences between the groups in the overall number of patients reporting adverse experiences during the study ($p > 0.05$). There was a tendency toward statistical significance ($p = 0.058$) for an increase in the incidence of dyspepsia in the r-HuEPO patients (7%) compared to the placebo-treated group (0%), 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, 23.9%; placebo, 26.2%), nausea (r-HuEPO, 22.4%; placebo, 38.5%), vomiting (r-HuEPO, 19.4%; placebo, 26.2%), fatigue (r-HuEPO, 16.4%; placebo, 18.5%), diarrhea (r-HuEPO, 14.9%; placebo, 6.2%), asthenia (r-HuEPO, 13.4%; placebo, 13.9%), edema (r-HuEPO, 13.4%; placebo, 9.2%), decreased appetite (r-HuEPO, 10.5%; placebo, 15.4%), bacterial infection (r-HuEPO, 10.5%; placebo, 10.8%), paresthesia (r-HuEPO, 10.5%; placebo, 7.7%), skin reactions at the injection site (r-HuEPO, 10.5%; placebo, 6.2%), abdominal pain (r-HuEPO, 10.5%; placebo, 4.6%), constipation (r-HuEPO, 10.5%; placebo, 4.6%), and rash (r-HuEPO, 10.5%; placebo, 3.1%).

Discontinuations due to adverse experiences. Seventeen patients (10 r-HuEPO, seven placebo) discontinued the double-blind treatment because of adverse experiences. One of these patients had an adverse experience that was characterized by the investigator as possibly related to therapy (#42732, placebo). Twelve (18%) r-HuEPO-treated patients discontinued study medication due to death, disease progression or adverse experiences versus 12 (18%) in the placebo group.

Deaths. Seven patients (three 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 nine patients (five r-HuEPO, four placebo) who participated in these studies reporting adverse experiences that required filing of an IND Safety Report to the FDA.

Antibody titers. Fifty patients (27 r-HuEPO, 23 placebo) who had a pre-and on-study determination did not exhibit a confirmed positive titer for anti-r-HuEPO antibodies. Four patients (one r-HuEPO, three placebo) had a positive titer either on Day 1 or both at Day 1 and on-study, suggesting a non-specific reaction to some component of the r-HuEPO formulation.

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 cyclic cisplatin-containing chemotherapy.

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