

Recombinant Human Erythropoietin Treatment for Chemotherapy-related Anemia in Children

Ali Varan, MD; Münevver Büyükpamukçu, MD; Tezer Kutluk, MD, PhD; and Canan Akyüz, MD

ABSTRACT. *Objective.* The efficacy and safety of recombinant human erythropoietin (rHuEPO) treatment in chemotherapy-induced anemia in children were investigated. rHuEPO is used to treat chemotherapy-induced anemia. Several studies recommend 150 to 300 IU/kg rHuEPO for 2 to 8 months. There are only a few controlled trials in children and no precise data about the optimal dose and duration of rHuEPO treatment is available.

Patients and Methods. Thirty-four patients receiving chemotherapy for treatment of their solid tumors between October 1996 and June 1997 were included in this study. Patients were randomly selected for each group. The male/female ratio was 20/14, and the median age was 5 years (range, 1–16 years). They had normal hemoglobin levels at the time of diagnosis. When hemoglobin levels decreased to levels lower than 10 g/dL, rHuEPO (150 IU/kg/d, 3 times a week, subcutaneously) was given to 17 patients for 2 months. Their renal, liver, and pulmonary functions were normal. None of the patients had hematologic disease. We did not use any other drugs such as iron or granulocyte colony-stimulating factor. There were 17 patients in the control group. Fifteen patients got chemotherapy regimens including cisplatin (CDDP), but 19 were treated with regimens without CDDP. At the end of rHuEPO treatment, all patients were examined in terms of transfusion requirements and rate of change in hemoglobin levels.

Results. One patient in the study group needed a blood transfusion, whereas 8 patients needed a transfusion in the control group. Patients in the study group had less transfusion requirements compared with the control group. The mean hemoglobin levels before and after the study were 8.48 ± 0.98 g/dL and 8.41 ± 1.65 g/dL in the control group and 8.50 ± 0.85 g/dL and 10.21 ± 2.14 g/dL in the rHuEPO group, respectively. Optimal hemoglobin increments began in 4 weeks and continued during treatment. CDDP-receiving and CDDP-nonreceiving groups did not have any difference in pretreatment serum erythropoietin levels. rHuEPO treatment was more effective in patients treated with non-CDDP regimens. Mean hemoglobin level increased from 8.68 ± 0.73 g/dL to 10.26 ± 1.84 g/dL in 9 patients treated with non-CDDP chemotherapy regimens in the erythropoietin group, although it increased from 8.28 ± 0.97 g/dL to 10.15 ± 2.5 g/dL in 8 patients treated with CDDP-containing regimens in the erythropoietin group. rHuEPO caused high blood pres-

sure in only 1 patient that resolved spontaneously after cessation of erythropoietin treatment for a week.

Conclusion. rHuEPO treatment (150 IU/kg/d 3 times a week) is effective and safe in children with chemotherapy-induced anemia. It decreases blood transfusion requirements in solid tumor patients. Our results show that the response to rHuEPO in CDDP-induced anemia is less than the response in non-CDDP receiving patients. Higher doses may be necessary in patients using CDDP. *Pediatrics* 1999;103(2). URL: <http://www.pediatrics.org/cgi/content/full/103/2/e16>; erythropoietin, solid tumors, chemotherapy, anemia, children.

ABBREVIATIONS. rHuEPO, recombinant human erythropoietin; CDDP, cisplatin.

Anemia in cancer patients has several causes, such as bone marrow suppression from chemotherapy, anemia of chronic disease, hemolysis, and erythropoietin deficiency because of chemotherapy-induced nephrotoxicity.^{1,2} Recombinant human erythropoietin (rHuEPO) is proposed to treat chemotherapy-induced anemia for reducing transfusion risks. Some authors stressed that regimens containing cisplatin (CDDP) lead to decreased erythropoietin production because of direct toxic effects on renal cells.^{3,4} Several studies showed efficacy of rHuEPO in these patients.^{2,5,6} Serum erythropoietin levels were found to be normal, low, or high in these studies. Different studies recommend 150 to 300 IU/kg rHuEPO for 4 to 8 months.^{5–7} There are only a few controlled trials in children and no precise data about the optimal dose and duration of rHuEPO treatment is available.^{8–10} The aim of our study is to investigate the efficacy and safety of rHuEPO in chemotherapy-induced anemia in children.

PATIENTS AND METHODS

Patients

Thirty-four patients admitted to our department between October 1996 and June 1997 were included in this study. There were 20 boys and 14 girls with a median age of 5 years (range, 1–16 years). Patients were randomly assigned to either the erythropoietin-receiving group or the control group. At the beginning of the study, an informed consent was obtained from all patients' parents after an explanation about the study. The types of malignant diseases in patients are given in Table 1. We put the patients on different chemotherapeutic regimens including cisplatin, vincristine, cyclophosphamide, (lomustine-1-(2-chloroethyl)-3 cyclohexyl-1-nitrosourea), procarbazine, actinomycin D, adriamycin, etoposide, dacarbazine, or high-dose methotrexate (in lymphoma patients) according to tumor subtype. Patients with Wilms' tumor, Ewing's sarcoma, rhabdomyosarcoma, or nasopharyngeal carcinoma also had local regional radiotherapy. Cranial and/or spinal

From the Department of Pediatric Oncology, Hacettepe University, Institute of Oncology, Ankara, Turkey.

Received for publication Mar 13, 1998; accepted Aug 27, 1998.

Reprint requests to (A.V.) Pediatric Oncologist, Department of Pediatric Oncology, Hacettepe University Institute of Oncology, 06100 Ankara, Turkey.

PEDIATRICS (ISSN 0031 4005). Copyright © 1999 by the American Academy of Pediatrics.

TABLE 1. Patients' Diagnoses

Lymphoma	7
Brain tumor	7
Astrocytoma	1
Medulloblastoma	4
Ependymoma	2
Rhabdomyosarcoma	5
Wilms' tumor	5
Neuroblastoma	2
Liver tumor	2
Ewing's sarcoma	2
Nasopharyngeal carcinoma	1
Retinoblastoma	1
Yolk sac tumor	2

radiotherapy was applied to brain tumors according to treatment protocols. Physical examinations and blood pressure measurements were made weekly. Serum erythropoietin levels were measured at the beginning of the study in all patients and were repeated again in the rHuEPO-treated group at the end of study. Complete blood counts were performed weekly. rHuEPO was given to 17 patients for a period of 2 months. Seventeen patients were in the control group. Fifteen patients received CDDP-containing regimens and 19 patients were treated with regimens without CDDP. In the CDDP group, patients continued to have normal renal function during the treatment course.

Inclusion Criteria

The patients who fulfilled the following criteria were included in the study: a) the patients' hemoglobin levels were >11 g/dL at the time of first admission. All patients had chemotherapy regimens because of primary malignant disease. Hemoglobin levels should be <10 g/dL at the beginning of this study. b) The hepatic, renal, and pulmonary functions were normal. c) All hematologic parameters including reticulocyte count, iron, iron-binding capacity, serum ferritin level, direct Coombs test, vitamin B₁₂ and folate levels, and arterial pH and blood gases were normal. d) The patients who received blood transfusions during the last month before onset of rHuEPO treatment were not included.

Treatment Regimen

rHuEPO was given at a 150 IU/kg/dose, 3 times a week, subcutaneously (rHuEPO was supplied partly by Cilag Inc (Zug, Switzerland) and marketed as EPREX) in 17 patients. If a patient had any of the complications of rHuEPO treatment such as hypertension, flushing, or deep vein thrombosis, drug administration was stopped. Patients with hemoglobin levels <6 g/dL and/or symptoms of anemia were given blood transfusions. At the end of 2 months, transfusion requirements and hemoglobin measurements were compared in the study and control groups. During the treatment period we did not use any other drugs such as granulocyte colony-stimulating factor or iron that could affect the hemoglobin response.

Statistical Methods

χ^2 was used to compare transfusion requirements between the study group and the control group. We compared the differences of the erythropoietin and hemoglobin levels in patients treated with and without CDDP by Mann-Whitney *U* test. The Wilcoxon test was used to determine the significance of hemoglobin increments.

RESULTS

Chemotherapy intensities in study and control groups were compared by analyzing the absolute neutrophil and thrombocyte counts and there was no significant difference ($P = .56, P = .55$, respectively). At the onset of treatment, serum erythropoietin levels of all patients were found to be between 14 and 410 IU/L (median, 70 IU/L), and there was no difference between the rHuEPO group and the control group in terms of serum erythropoietin levels ($P =$

TABLE 2. Patient Characteristics in Study and Control Groups

	rHuEPO Group	Control Group
Number of patients	17	17
Mean Hb level (g/dL)		
At the beginning of the study	8.50 ± 0.85	8.48 ± 0.98
At the end of the study	10.21 ± 2.14	8.41 ± 1.65
<i>P</i> value	.0086	.90
Median erythropoietin levels (IU/L)		
At the beginning	80 (14–410)	62 (19–270)
At the end of the study	22 (3.5–270)	Not done
Number of transfusion requirements	1	8

Abbreviation: rHuEPO, recombinant human erythropoietin.

.52; Table 2). This was also true for CDDP and non-CDDP groups ($P = .14$). The erythropoietin levels at the beginning were higher than the levels after erythropoietin treatment in the study group.

There was no difference in initial hemoglobin levels between rHuEPO and non-rHuEPO groups ($P = .95$). The difference between the Hb levels of both groups at the end of the study was statistically significant (10.21 g/dL vs 8.41 g/dL; $P = .027$; Table 2). The mean hemoglobin levels before and after the study were 8.48 ± 0.98 g/dL and 8.41 ± 1.65 g/dL ($P = .9$) in the control group. The mean hemoglobin level in the rHuEPO-treated group was 8.50 ± 0.85 g/dL before treatment and it increased to the level of 10.21 ± 2.14 g/dL ($P = .0086$) after rHuEPO treatment. The increase in hemoglobin levels began 4 weeks after onset of treatment and continued progressively in the rHuEPO group. Hemoglobin levels at 2, 4, 6, and 8 weeks were 8.85 ± 1.25, 9.27 ± 1.8, 9.83 ± 1.58, 10.21 ± 2.14 g/dL, respectively (Fig 1). These results were 8.71 ± 1.33, 8.62 ± 1.25, 8.99 ± 1.30, and 8.41 ± 1.65 g/dL in the control group, respectively. rHuEPO treatment was more effective in the erythropoietin group receiving the non-CDDP regimen. Mean hemoglobin level increased from 8.68 ± 0.73 g/dL to 10.26 ± 1.84 g/dL ($P = .038$) in 9 patients treated with the non-CDDP chemotherapy regimen, although it increased from 8.28 ± 0.97 g/dL to 10.15 ± 2.5 g/dL in 8 patients in the erythropoietin group treated with CDDP-containing regimens ($P = .28$; Table 3).

During the treatment period, 1 patient in the rHuEPO group and 8 patients in the control group needed blood transfusions. This is statistically signif-

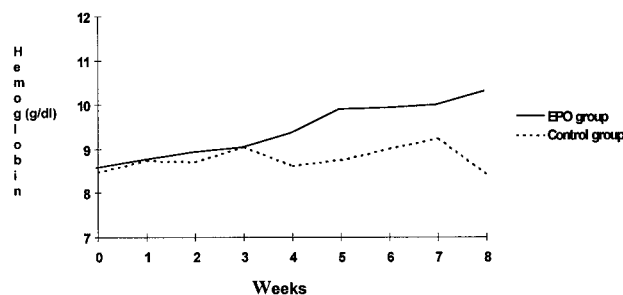


Fig 1. Hemoglobin levels during the study in the erythropoietin and control groups.

TABLE 3. Patient Characteristics in rHuEPO Group Treated With CDDP or Non-CDDP-containing Regimens

	CDDP Group	non-CDDP Group
Number of patients	8	9
Mean Hb level (g/dL)		
At the beginning of the study	8.28 ± 0.97	8.68 ± 0.73
At the end of the study	10.15 ± 2.5	10.26 ± 1.84
<i>P</i> value	.12	.038

Abbreviations: rHuEPO, recombinant human erythropoietin; CDDP, cisplatin.

icant ($P = .008$). Before onset of the study, in the rHuEPO group 3 patients needed a blood transfusion once and 3 patients needed a blood transfusion twice; and transfusion requirements were once in 2 patients and twice in 2 patients for the control group.

We observed only one complication in the rHuEPO group. This patient had high blood pressure after 2 weeks of rHuEPO treatment. We stopped rHuEPO treatment for a week and blood pressure returned to normal levels. rHuEPO was started again with no increase in blood pressure.

DISCUSSION

It is well-known that blood transfusions may cause many complications such as infections (HIV, hepatitis B, cytomegalovirus, etc.), iron loading, and hemolytic reactions. Use of recombinant growth factor is thought to reduce these adverse reactions by decreasing transfusion requirements. Most of rHuEPO studies are related with adult cases.^{2,5-7,11,12} Firstly, Miller and coworkers⁵ mentioned that adult patients who had received high rHuEPO doses (100–200 IU/kg) showed a good response. Dunphy et al⁶ reported that the rHuEPO dose should be increased in patients who used paclitaxel and carboplatin if the response was inadequate with 150 IU/kg.

There are a few studies about rHuEPO treatment in children, and the optimal dose of rHuEPO is not defined precisely.⁸⁻¹⁰ Nenadov Beck et al⁹ used low doses of rHuEPO for 2 weeks and did not see any response in pediatric cases. This period is very short and inadequate for evaluation of rHuEPO treatment. They used a maximum of 100 IU/kg rHuEPO, lower than other studies. Most of the studies recommend rHuEPO treatment for 2 or 3 months in chemotherapy-induced anemia of solid tumors. Porter et al⁸ mentioned that a starting dose of 150 IU/kg was administered to their pediatric patients with a median dose of 198 IU/kg rHuEPO per dose. They increased the rHuEPO dose if the patients had blood transfusions or inadequate response. They found that a 16-week treatment with rHuEPO decreased the requirement for platelet transfusion. Our results were similar to this controlled trial for blood transfusion requirements. In our study, we used 150 IU/kg rHuEPO for 2 months without giving any iron supplement. Optimal results were obtained in 4 weeks and continued during treatment. In another study, León et al¹³ applied 150 IU/kg rHuEPO 5 times weekly for 3 months, but they used historical controls and performed red cell transfusions if the Hb level was lower than 9 g/dL. Historical controls

have some disadvantages such as case selection bias. We observed a significant decrease in the transfusion requirement with the use of rHuEPO (8 vs 1 patient needed transfusions in the control group and the rHuEPO group, respectively). This finding suggests that rHuEPO, 150 IU/kg for 2 months, can be used effectively for treatment of chemotherapy-related anemia in children with malignancy. A good response was achieved in 4 weeks. The significant difference on the hemoglobin levels of the study and the control groups also confirmed the efficacy of rHuEPO treatment in our patients. Transfusion was done if Hb levels were lower than the 6 g/dL in our study to detect the difference between both groups. This cutoff level was relatively higher in other studies, eg, 9 g/dL in one study¹³ and 8 g/dL in another study.⁸ We believe that the higher cutoff level may shadow the real difference between the erythropoietin-treated and the erythropoietin-untreated groups. The decrease of high erythropoietin levels to normal levels in the rHuEPO-treated group also could be attributable to both normalization of Hb levels (endogenous cause) and suppression of erythropoietin synthesis by rHuEPO (exogenous cause).

Some authors reported that patients using CDDP had inadequate response to erythropoietin as a result of nephrotoxicity.^{4,14} Although there is no significant difference on erythropoietin levels of patients treated with and without CDDP-containing regimens, response to rHuEPO was better in patients treated with non-CDDP-containing regimens. Miller et al⁵ investigated whether rHuEPO affected CDDP-induced anemia or not. They found out that rHuEPO, 100 to 200 IU/kg, were useful in those cases, but their study was only a single arm, dose escalation phase I-II study. In Cascinu's² study, 100 patients who received cisplatin were randomly assigned to either erythropoietin or nonerythropoietin groups. They compared rHuEPO and placebo, but their study did not include patients who had a non-CDDP-containing regimen. In our study, the Wilcoxon *P* values for hemoglobin increments of CDDP and non-CDDP groups in the erythropoietin group were .12 and .038, respectively. This difference may be decreased by giving higher rHuEPO doses. Bone marrow may not respond adequately because of the myelosuppressive effect of CDDP.⁴ The anemia of our patients improved after rHuEPO treatment. We suggest that patients using CDDP should be treated with higher dosages of rHuEPO when needed. The number of patients in the CDDP group is relatively less and further studies with a greater number of patients and different erythropoietin doses should be done.

We observed that 1 patient transiently had high blood pressure during rHuEPO treatment. After cessation of the rHuEPO for 1 week, blood pressure returned to normal and we continued rHuEPO without any complications. Most of the studies report few complications with this drug. Deep vein thrombosis, flushing, polycythemia, and high blood pressure are among the reported complications.^{5,7,8,12} We did not observe any of these complications.

We conclude that rHuEPO treatment is effective and safe in minimizing transfusion requirements in

children with solid tumors at doses of 150 IU/kg given three times a week for 2 months. Higher doses may be necessary in patients using CDDP. Because chemotherapy-induced anemia is related to inadequate response to high endogenous erythropoietin, cancer patients may benefit from exogenous rHuEPO during chemotherapy.

REFERENCES

1. Henry DH. Clinical application of recombinant erythropoietin in anemic cancer patients. *Hematol Oncol Clin North Am.* 1994;8:961–973
2. Cascinu S, Fedeli A, Del Ferro E, Fedeli SL, Catalano G. Recombinant human erythropoietin treatment in cisplatin-associated anemia: a randomized, double-blind trial with placebo. *J Clin Oncol.* 1994;12:1058–1062
3. Lelieveld P, Van Der Vijgh WJF, Veldhuizen RW, et al. Preclinical studies on toxicity, antitumour activity and pharmacokinetics of cisplatin and three recently developed derivatives. *Eur J Clin Oncol.* 1984;20:1087–1104
4. Rhotmann SA, Paul P, Weick JK, McIntyre WR, Fantelli F. Effect of cis-diamminedichloroplatinum on erythropoietin production and hematopoietic progenitor cells. *Int J Cell Cloning.* 1985;3:415–423
5. Miller CB, Plataniias LC, Mills SR, et al. Phase I-II trial of erythropoietin in the treatment of cisplatin-associated anemia. *J Natl Cancer Inst.* 1992;84:98–103
6. Dunphy FR, Dunleavy TL, Harrison BR, et al. Erythropoietin reduces anemia and transfusions after chemotherapy with paclitaxel and carboplatin. *Cancer.* 1997;79:1623–1628
7. Plataniias LC, Miller CB, Mick R, et al. Treatment of chemotherapy-induced anemia with recombinant human erythropoietin in cancer patients. *J Clin Oncol.* 1991;9:2021–2026
8. Porter JC, Leahey A, Polise K, Bunin G, Manno CS. Recombinant human erythropoietin reduces the need for erythrocyte and platelet transfusions in pediatric patients with sarcoma: a randomized double-blind, placebo controlled trial. *J Pediatr.* 1996;129:656–660
9. Nenadov Beck M, Beck D. Recombinant erythropoietin in acute chemotherapy-induced anemia of children with cancer. *Med Pediatr Oncol.* 1995;25:17–21
10. Bolonaki I, Stiakaki E, Lydaki E, et al. Treatment with recombinant human erythropoietin in children with malignancies. *Pediatr Hematol Oncol.* 1996;13:111–121
11. Ludwig H, Fritz E, Kotzman H, Höcker P, Gisslinger H, Barnas U. Erythropoietin treatment of anemia associated with multiple myeloma. *N Engl J Med.* 1990;322:1693–1699
12. Cascinu S, Fedeli A, Fedeli SL, Catalano G. Cisplatin associated anaemia treated with subcutaneous erythropoietin. A pilot study. *Br J Cancer.* 1993;67:156–158
13. León P, Jiménez M, Barona P, Sierrasesúмага L. Recombinant human erythropoietin for the treatment of anemia in children with solid malignant tumors. *Med Pediatr Oncol.* 1998;30:110–116
14. Miller CB, Jones RJ, Piantadosi S, Abeloff MD, Spivak JL. Decreased erythropoietin response in patients with the anemia of cancer. *N Engl J Med.* 1990;322:1689–1692

Recombinant Human Erythropoietin Treatment for Chemotherapy-related Anemia in Children

Ali Varan, Münevver Büyükpamukçu, Tezer Kutluk and Canan Akyüz

Pediatrics 1999;103:e16

DOI: 10.1542/peds.103.2.e16

Updated Information & Services

including high resolution figures, can be found at:
<http://pediatrics.aappublications.org/content/103/2/e16>

References

This article cites 14 articles, 2 of which you can access for free at:
<http://pediatrics.aappublications.org/content/103/2/e16#BIBL>

Subspecialty Collections

This article, along with others on similar topics, appears in the following collection(s):
Hematology/Oncology
http://www.aappublications.org/cgi/collection/hematology:oncology_sub

Permissions & Licensing

Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
<http://www.aappublications.org/site/misc/Permissions.xhtml>

Reprints

Information about ordering reprints can be found online:
<http://www.aappublications.org/site/misc/reprints.xhtml>

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™



PEDIATRICS®

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Recombinant Human Erythropoietin Treatment for Chemotherapy-related Anemia in Children

Ali Varan, Münevver Büyükpamukçu, Tezer Kutluk and Canan Akyüz

Pediatrics 1999;103:e16

DOI: 10.1542/peds.103.2.e16

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://pediatrics.aappublications.org/content/103/2/e16>

Pediatrics is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. Pediatrics is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 1999 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 1073-0397.

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™

