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Is Epoetin Alfa a Treatment Option for Chemotherapy-Related Anemia in Children?

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Background. The efficacy and safety of epoetin alfa in ameliorating cancer- or chemotherapy-related anemia and reducing red blood cell (RBC) transfusion requirements have been demonstrated in numerous trials in adult patients. However, limited information is available about recombinant human erythropoietin (rHuEPO, epoetin alfa) as a treatment option in pediatric cancer patients. ***Procedure.*** To gain more information about the efficacy and safety of epoetin alfa in the treatment of chemotherapy-induced anemia in children with solid tumors receiving either platinum- or nonplatinum-containing chemotherapy, an 8-week randomized trial was conducted. Epoetin alfa 150 IU/kg was given 3 times a week for 8 weeks to 17 patients; 17 control patients received standard of care. ***Results.*** Transfusions, administered if the hemoglobin (Hb) level dropped to below 6 g/dL, were necessary for only one patient in the epoetin alfa group, as compared with eight patients in the control group (change in Hb from 8.5–10.21 g/dL in the epoetin alfa group vs. 8.48–8.41 g/dL in the control group). ***Conclusions.*** The data from this study suggest that this dosing regimen of epoetin alfa is effective and safe in pediatric cancer patients with chemotherapy-related anemia. Further studies with epoetin alfa in more children with different chemotherapy regimens are needed. Med Pediatr Oncol 2002;39:455–458.

Key words: anemia; epoetin alfa; chemotherapy complications; childhood cancer

INTRODUCTION

Anemia is a common, multifactorial complication in cancer patients and may be caused by bone marrow suppression, hemolysis, anemia of chronic disease, inadequate erythropoietin production, hemorrhage, and chemotherapy. Red blood cell (RBC) transfusions have been thus far the anemia treatment of choice but are associated with adverse effects, such as the transmission of infectious agents, hemolytic reactions, and iron overload. The introduction of recombinant human erythropoietin (rHuEPO, epoetin alfa) introduced a new option for the treatment of cancer-associated anemia. In adult cancer patients, epoetin alfa has been effective in reducing the need for RBC transfusions, increasing hemoglobin (Hb) levels, and improving the overall quality of life (QOL). This has been shown in numerous studies in patients undergoing chemotherapy for solid tumors and hematologic malignancies, including randomized, double-blind, placebo-controlled trials [1,2], and large, community-based clinical trials [3–5]. In these studies, epoetin alfa was well tolerated. The benefits of epoetin alfa treatment for adult anemic cancer patients are thus well documented, but is epoetin alfa a treatment option for cancer- or chemotherapy-related anemia in children?

There is only limited information available about the efficacy of epoetin alfa, its safety, and optimal dose and duration of treatment in children with cancer receiving chemotherapy. The few studies published to date describe a variety of epoetin alfa dosing regimens across the range of 150–450 IU/kg with treatment duration ranging from 2 weeks to 8 months [6–11]. These studies showed promising results, indicating that epoetin alfa may be a treatment option for cancer- or chemotherapy-related anemia in children. A recent randomized trial in children with solid tumors and chemotherapy-induced anemia receiving epoetin alfa further supported these findings [12]. The results and conclusions of this study are presented in this study.

PATIENTS AND STUDY DESIGN

Patients had to present with normal hepatic, renal, and pulmonary functions, and normal hematologic parameters, as well as Hb levels > 11 g/dL at time of first

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admission, to be included in the study. They received chemotherapy for primary malignant disease; Hb levels had to drop below 10 g/dL before study entry. Patients who received RBC transfusions during the last month before the onset of the study were excluded. Thirty-four patients, 14 girls and 20 boys with a median age of 5 years (range 1–16) diagnosed with various solid tumors were randomly assigned to either the epoetin alfa group (17 patients) or control group (17 patients) (Table I). Chemotherapy regimens were platinum- and nonplatinum-based and patients with certain tumor types received radiotherapy (Table II). Physical examinations, blood counts, and blood pressure measurements were performed weekly. Serum erythropoietin (EPO) levels were measured at the beginning of the study in all patients and at the end of the study in epoetin alfa patients. Epoetin alfa was administered at a dose of 150 IU/kg, three times a week (tiw), subcutaneously (sc) for 2 months. In the event of complications (deep vein thrombosis, hypertension, flushing), epoetin alfa was withdrawn. Transfusions were administered if Hb levels dropped below 6 g/dL. No iron supplementation or granulocyte colony-stimulating factor was given to the patients during the study period.

RESULTS

Hematologic Parameters

To compare chemotherapy intensities in the epoetin alfa and control groups, the absolute neutrophil and thrombocyte counts were analyzed; no significant difference was observed. There was also no significant difference between the epoetin alfa and control groups regarding serum EPO levels (14–410 IU/L, median 80 IU/L vs. 19–270 IU/L, median 62 IU/L, respectively). Median EPO levels in the epoetin alfa group, however, were lower at study end when compared to study entry (14–410 IU/L, median 80 IU/L vs. 3.5–270 IU/L, median 22 IU/L, respectively) (Table III).

Hemoglobin Levels

There was no significant difference in initial mean Hb levels at study entry between the epoetin alfa and the control groups (8.5 g/dL vs. 8.48 g/dL, respectively). However, at the end of the study, a significant ($P = .027$) difference in mean Hb was observed between the two groups (10.21 g/dL vs. 8.41 g/dL, respectively) (Table III). Analysis of mean Hb over the course of the study showed a significant ($P = .0086$) increase in the epoetin alfa group from 8.50 to 10.21 g/dL. This increase became apparent after 4 weeks of treatment and continued progressively to study end. On the other hand, in the control group, mean Hb levels did not change significantly from study start to study end (8.48 g/dL vs. 8.41 g/dL, respectively) (Fig. 1).

TABLE I. Demographics and Clinical Characteristics

	Total study population (N = 34)	
Sex, n (%)		
Female	14 (41.2)	
Male	20 (58.8)	
Age (years)		
Median	5	
Range	1–16	
Diagnosis	Epoetin alfa group (n = 17)	Control group (n = 17)
Tumor type, n (%)		
Lymphoma	3 (17.6)	4 (23.5)
Brain tumor[a]	5 (29.4)	2 (11.7)
Rhabdomyosarcoma	3 (17.6)	2 (11.7)
Wilms tumor	1 (5.9)	4 (23.5)
Neuroblastoma	1 (5.9)	1 (5.9)
Liver tumor	1 (5.9)	1 (5.9)
Ewing sarcoma	0 (0.0)	2 (11.7)
Nasopharyngeal carcinoma	1 (5.9)	0 (0.0)
Retinoblastoma	1 (5.9)	0 (0.0)
Yolk sac tumor	1 (5.9)	1 (5.9)

[a]Including astrocytoma, medulloblastoma, and ependymoma.

TABLE II. On-Study Cancer Treatments (N = 34)

Platinum-based chemotherapy, n (%)	15 (44.1)
Nonplatinum-based chemotherapy, n (%)	19 (55.9)
Local regional radiotherapy, n (%)	13 (38.2)[a]
Cranial and/or spinal radiotherapy, n (%)	7 (20.6)[b]

[a]Patients with rhabdomyosarcoma, Wilms tumor, Ewing sarcoma, and nasopharyngeal carcinoma.
[b]Patients with brain tumors.

TABLE III. Endogenous EPO, Hb Levels, and Transfusion Requirements

	Epoetin alfa group (n = 17)	Control group (n = 17)
Median EPO levels (IU/L)		
Study start	80	62
Study end	22	Not done
Mean Hb levels (g/dL)		
Study start	8.50	8.48
Study end[a]	10.21	8.41
Number of transfusions required[b]	1	8

EPO, erythropoietin; Hb, hemoglobin.
Adapted and Reproduced with permission from *Pediatrics*, Vol. 103, Pages C16–C19, Table II, Copyright 1999 [12].
[a]$P = .027$, between-group difference.
[b]$P = .008$, between-group difference.

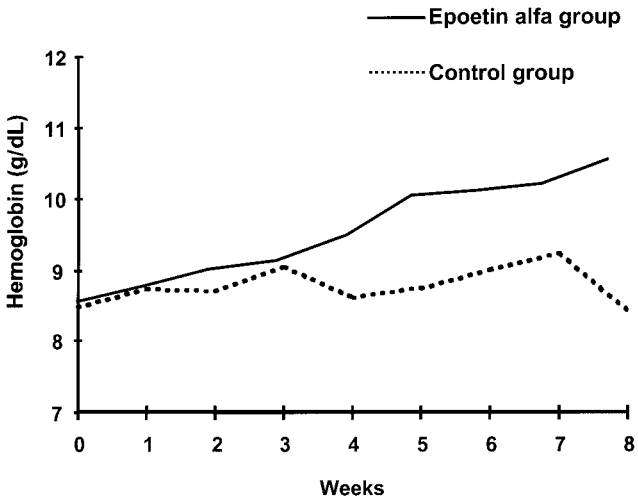

Fig. 1. Hemoglobin levels during the course of the study. Hemoglobin levels start to increase in epoetin alfa patients after 4 weeks of therapy. Solid line: epoetin alfa group (n = 17); dashed line: control group (n = 17). Reproduced with permission from *Pediatrics*, Vol. 103, Pages C16–C19, Figure 1, Copyright 1999.

RBC Transfusion Requirements

Analysis of transfusion requirements showed that significantly ($P = .008$) fewer patients in the epoetin alfa group required transfusions over the course of the study when compared to the control group (5.9% vs. 47.0%, respectively) (Table III). Red blood cell transfusions prior to 1 month before the onset of the study were given once to three patients and twice to three patients in the epoetin alfa group. Two control patients received transfusion once, and two control patients twice before entering the study.

Safety

One patient developed hypertension after 2 weeks of epoetin alfa treatment. Epoetin alfa therapy was stopped until blood pressure returned to normal levels. The epoetin alfa treatment was continued after 1 week without further complications.

DISCUSSION

The efficacy and safety of epoetin alfa in treating cancer- or chemotherapy-related anemia in adult patients is well documented. Increases in Hb levels, reductions in transfusion requirements, and overall improvement in QOL have been reported [1–5]. Most of these studies reported administration of epoetin alfa 150 or 300 IU/kg tiw, which was well tolerated. Recently, 40,000–60,000 IU administered once weekly was shown to be similar in efficacy and safety to tiw administration [5]. However, little information is available to date about the efficacy and safety of epoetin alfa in pediatric patients. Trials conducted in children are described in detail by Feusner and Hastings elsewhere in this supplement.

The study conducted by Varan et al. [12] showed that a dose of epoetin alfa 150 IU/kg tiw for 8 weeks significantly increased Hb levels in pediatric cancer patients with chemotherapy-associated anemia. Response to treatment was observed after 4 weeks of treatment, a trend that continued progressively until the end of the study. Hemoglobin levels increased in epoetin alfa patients regardless of platinum- or nonplatinum-based chemotherapy. Additionally, transfusion requirements were significantly reduced in epoetin alfa patients when compared to control patients. Epoetin alfa was well tolerated.

CONCLUSIONS

Epoetin alfa therapy was well tolerated, led to increased Hb levels, and minimized RBC transfusion requirements in children with solid tumors with chemotherapy-induced anemia. Further studies of epoetin alfa in children receiving a variety of anticancer chemotherapy regimens are warranted.

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