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Early Epoetin Alfa Treatment in Children With Solid Tumors

Andreas Zoubek, MD* and Martina Kronberger, MD

Background. Combination chemotherapy is often used for long periods in children with solid malignancies, leading to anemia and necessitating intervention with red blood cell (RBC) transfusions. Transfusions, however, are associated with a variety of adverse events and risks. Recombinant human erythropoietin (rHuEPO, epoetin alfa) has been shown to reduce the need for transfusions and to ameliorate the symptoms of anemia in adults, but few studies have been conducted thus far in pediatric patients. ***Procedure.*** Thirty-seven children with solid tumors receiving treatment with platinum- or nonplatinum-based chemotherapy were treated with epoetin alfa and supplemental iron in a single-center, open-label, 28-week, case-control study. ***Results.*** Epoetin alfa significantly reduced the need for RBC ($P = 0.007$) and platelet ($P = 0.01$) transfusions, and prolonged the time to first RBC transfusion ($P = 0.0004$) as compared to the control group. Moreover, epoetin alfa was effective in maintaining mean hemoglobin levels during the course of the study, whereas they declined below baseline after week 9 in the control group. ***Conclusions.*** Epoetin alfa is effective and safe in reducing transfusion requirements and maintaining adequate hemoglobin levels in children with solid tumors undergoing combination chemotherapy. Med Pediatr Oncol 2002; 39:459–462.

Key words: pediatric; anemia; epoetin alfa; transfusion; solid tumors

INTRODUCTION

Children with cancer often receive high-dose combination chemotherapy for an extended period of time. As a result, the prognosis for pediatric patients with cancer is positive and 5-year survival rates ranging from 50% to 90% have been observed [1–3]. However, this more aggressive approach leads to substantial myelosuppression, leaving children severely anemic. The use of platinum-based chemotherapy might further exacerbate the symptoms of anemia due to toxic effects on renal cells [4,5].

To ameliorate the symptoms of anemia and increase hemoglobin (Hb) levels, red blood cell (RBC) transfusions have been the conventional treatment. Unfortunately, RBC transfusions are associated with numerous adverse events and risks. The transmission of infectious agents and immunosuppression are consequences of RBC transfusion treatment [6–10]. In light of the good prognosis and survival rates in children with cancer, the possible lifelong consequences of these adverse events are of major concern. In particular, transmission of the hepatitis C virus (HCV) still represents a serious threat to children receiving transfusions. For instance, HCV-related liver disease developed in 35 of 65 transfused pediatric cancer patients enrolled in a study by Strickland et al. [6]. Liver biopsy in these 35 patients showed that 28 patients (80%) had chronic active hepatitis, 25 (71%) had fibrosis, and 3 (9%) had cirrhosis [6]. For these reasons, clinicians might hesitate to administer RBC transfusions to anemic children with cancer, since these patients can anticipate a normal life span if cured of their cancer. The symptoms of anemia therefore often remain untreated, which causes an unnecessary burden to children with cancer undergoing chemotherapy.

Administration of recombinant human erythropoietin (rHuEPO, epoetin alfa) has been shown to reduce the need for RBC transfusions and to guarantee the safest and most effective anemia treatment. Studies in adult cancer patients have shown that epoetin alfa increases Hb levels, reduces transfusion requirements, ameliorates the symptoms of anemia, and improves quality of life [11–16]. To date, few studies are available on epoetin alfa in children with cancer [17–23]. Two of these studies are of particular interest. Porter et al conducted a double-blind, placebo-controlled study in which epoetin alfa-treated patients required fewer RBC and platelet transfusions compared to the control group [21]. Varan et al. showed that the administration of epoetin alfa reduced transfusion needs and increased Hb levels after 2 months [23].

A small pilot study conducted at the St. Anna Children's Hospital in Vienna also showed encouraging results. Children with solid tumors receiving epoetin alfa required fewer units of RBC transfusions and had higher median Hb levels compared to historic controls [19]. Based on these observations, the study was expanded and more children

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were included. The results of this recently published study [24] are summarized in this article.

STUDY DESIGN AND PATIENTS

Thirty-seven children, including the 10 children enrolled in the pilot study [19], participated in the single-center, open-label, 28-week, case-control study. The study population had a median age of 11.4 years (range 1–18 years), and included 19 (51.4%) males and 18 (48.6%) females. These children were being treated with either platinum-based (48.6%) or nonplatinum-based (51.4%) chemotherapy, and in addition, many had undergone surgery (91.9%) and radiation therapy (43.2%). The most common tumor types were osteosarcoma (40.6%), Ewing sarcoma (21.6%), and rhabdomyosarcoma (13.5%).

Starting with the first course of chemotherapy, epoetin alfa was administered three times a week (tiw), intravenously (IV) or subcutaneously (sc), at a dose of 150 IU/kg if Hb levels were $\geq$12 g/dL and $\leq$16 g/dL, or 300 IU/kg if Hb levels were $<$12 g/dL. The epoetin alfa dose was increased to 300 IU/kg when Hb levels decreased to $<$12 g/dL, and it was withdrawn when Hb levels exceeded 16 g/dL and then resumed after Hb decreased to $\leq$16 g/dL. Patients were excluded from the study if they had previous transfusions, severe infections within 7 days before study start, left ventricular hypertension, or non-tumor-related cerebral spasm.

All patients also received Fe^{2+} 5 mg/kg daily during therapy with epoetin alfa. RBC transfusions were administered when Hb levels reached 6.5 g/dl, or at higher levels if indicated by clinical symptoms of anemia such as tachypnea, tachycardia, or septicemia; or at the physician's discretion.

The efficacy of epoetin alfa was determined by evaluating RBC and platelet transfusion requirements, time to first transfusion, and changes in Hb levels. Comparisons were made with an historic control group of 37 children with solid malignancies, who did not receive epoetin alfa or iron supplementation during chemotherapy. This control group was generally comparable for sex, age, mean Hb levels at baseline, and on-study cancer treatment with the group receiving epoetin alfa. The safety of epoetin alfa was documented from the incidence of adverse events.

RESULTS

During the 28-week study, RBC transfusion requirements were significantly lower in the epoetin alfa group than in the control group. Overall, 62.2% of the patients

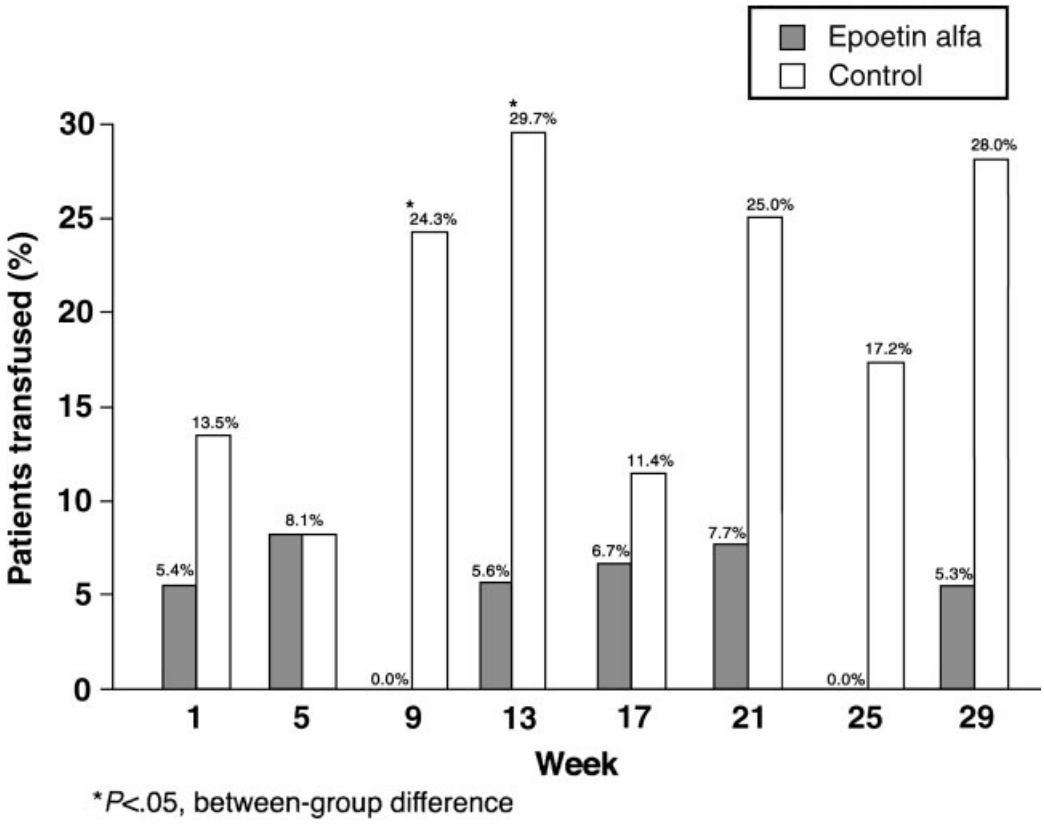


Fig. 1. Percentage of patients in the epoetin alfa and control group receiving RBC transfusions over the 28-week study period. Baseline = week 1 of chemotherapy. Copyright 2002 from ''Reduction in transfusion requirements with early epoetin alfa treatment in pediatric patients with solid tumors: A case-control study,'' by Kronberger et al. Reproduced by permission of Taylor & Francis, Inc., http://www.routledge.ny.com.

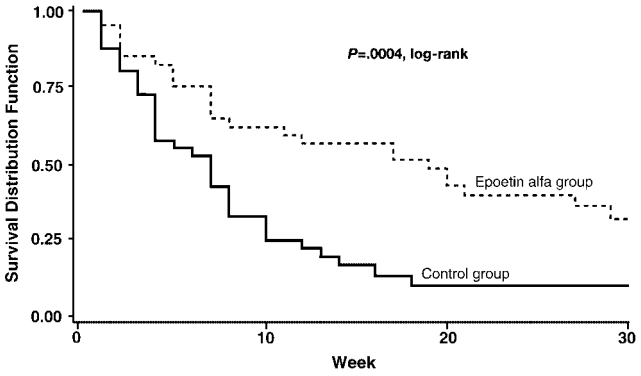
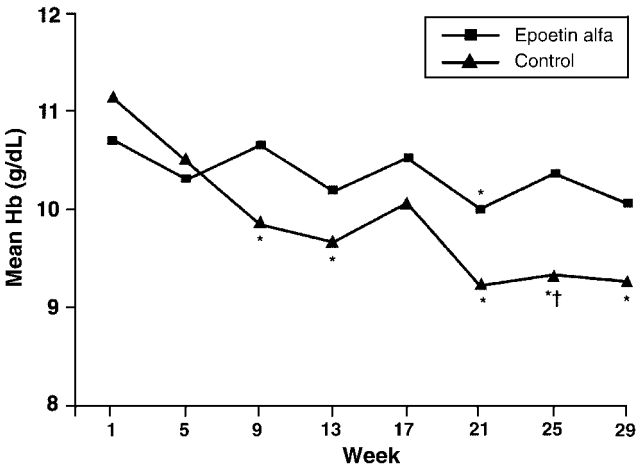


Fig. 2. Kaplan–Meier estimates of time to first RBC transfusion. Copyright 2002 from "Reduction in transfusion requirements with early epoetin alfa treatment in pediatric patients with solid tumors: A case-control study," by Kronberger et al. Reproduced by permission of Taylor & Francis, Inc., http://www.routledge.ny.com.

in the epoetin alfa group required RBC transfusions compared to 89.2% in the control group ($P = .007$). Differences between these groups in the percentage of patients requiring RBC transfusions were seen at most time points during the study (Fig. 1). On the basis of Kaplan–Meier estimates, the mean time to first RBC transfusion was significantly prolonged by epoetin alfa (10.1 vs. 5.9 weeks, $P = .0004$, log-rank test) (Fig. 2). In addition to the lower need for RBC transfusions, epoetin alfa significantly reduced platelet transfusions—35.1% in the epoetin alfa group compared to 64.9% in the control group ($P = .01$).

In the epoetin alfa group, Hb levels were maintained at baseline for most of the study, dropping significantly under baseline only at week 21 ($P < .02$) (Fig. 3). The mean change in Hb levels from baseline (10.8 g/dL) to final value (10.1 g/dL) was not statistically significant. In contrast, the decrease in mean Hb from baseline (11.1 g/dL) to final value (9.3 g/dL) was statistically significant in the control group ($P < .01$), with mean Hb levels falling below baseline starting at week 9 ($P < .02$). The efficacy of epoetin alfa was seen in children regardless of whether they were receiving platinum- or nonplatinum-based chemotherapy. Mean Hb levels were maintained by epoetin alfa in both subgroups, and only dropped under baseline at week 21 in the platinum group ($P = .049$). Moreover, the percentage of children requiring RBC transfusions did not differ significantly for those receiving platinum-based (55%) or nonplatinum-based (69%) chemotherapy ($P > .05$).



*P<.05, difference from baseline
†P<.05, between-group difference

Fig. 3. Mean Hb levels (g/dL) for epoetin alfa and control group over the 28-week study period. Baseline = week 1 of chemotherapy. Copyright 2002 from "Reduction in transfusion requirements with early epoetin alfa treatment in pediatric patients with solid tumors: A case-control study," by Kronberger et al. Reproduced by permission of Taylor & Francis, Inc., http://www.routledge.ny.com.

Epoetin alfa was well tolerated. Hb levels reached >16 g/dL in two patients, at which point epoetin alfa had to be withheld until after Hb levels decreased to ≤16 g/dL. Only one patient was withdrawn from epoetin alfa therapy (due to myocarditis). Two patients, a 16-year-old girl and a 15-year-old girl, developed deep vein thrombosis (DVT) during the course of the study. Both patients were immobilized due to osteogenic sarcoma of the pelvis and osteogenic sarcoma of the femur, respectively. The 16-year-old girl developed pulmonary, nonfatal embolism, and the 15-year-old girl's DVT developed into fatal pulmonary embolism. Both patients had Hb levels <12 g/dL and received epoetin alfa at a dosage of 300 IU/kg. All adverse events are summarized in Table I.

SUMMARY AND DISCUSSION

The results of this case-control study of 37 children [24] extend the findings of the pilot study [19]. Epoetin alfa was effective and safe in reducing the need for RBC and platelet transfusions in children with solid tumors who were undergoing either platinum-based or nonplatinum-based chemotherapy. Moreover, epoetin alfa maintained mean Hb levels at or near baseline over the course of the 28-week study. These findings confirm the results of two previous noteworthy studies. In a randomized controlled study of 24 children with solid malignancies, Porter et al. [21] showed that fewer RBC and platelet transfusions were needed with epoetin alfa therapy as compared to placebo. Similarly, Varan et al. [23] demonstrated that RBC transfusion requirements were significantly lower with epoetin alfa than control in a study of 34 pediatric patients with

TABLE I. Adverse Events Occurring in ≥5% of Patients

	Epoetin alfa (n = 37)	Control (n = 37)
Sepsis, n (%)	33 (89.2)	34 (91.9)
Mucositis, n (%)	6 (16.2)	3 (8.1)
Delayed methotrexate elimination, n (%)	4 (10.8)	0
Veno-occlusive disease, n (%)	0	3 (8.1)
Deep-vein thrombosis, n (%)	2 (5.4)	0

solid tumors receiving chemotherapy. In that study, patients receiving epoetin alfa achieved higher Hb levels after 4 weeks of treatment when compared to control patients [23].

The administration of epoetin alfa at a dosage of 150 IU/kg (Hb $\geq$12 g/dL and $\leq$16 g/dL) or 300 IU/kg (Hb $<$12 g/dL) to chemotherapy-naïve patients starting with the first course of chemotherapy appears to be effective in maintaining Hb levels. A significant decline in Hb levels below baseline was seen only at week 21 in the epoetin alfa group, whereas it dropped under baseline at week 9 in the control group. On the basis of these observations, it appears that early administration of epoetin alfa, starting with the first course of chemotherapy, is sufficient in preventing a decrease in Hb levels during chemotherapy. However, trials involving greater numbers of children will be necessary to determine the optimal epoetin alfa dose as well as the right time point to start epoetin alfa therapy.

The benefit of epoetin alfa in reducing RBC transfusion requirements and increasing mean Hb levels was seen regardless of whether the children received platinum-based or nonplatinum-based chemotherapy. Small differences between these subgroups of children were not of statistical significance. This finding supports the results observed in trials conducted in adult cancer patients where epoetin alfa showed similar efficacy in patients receiving platinum- and nonplatinum-based chemotherapy regimens [12,13,15].

In summary, epoetin alfa was shown to be effective and safe in children with solid tumors undergoing chemotherapy. However, few trials have been conducted to date on epoetin alfa in children and more studies with larger numbers of children are warranted. It will be necessary to evaluate the optimal dose and duration of epoetin alfa therapy as well as criteria for identifying children likely to respond. Randomized, controlled trials are currently underway to further investigate the optimal usage of epoetin alfa in children and to confirm the positive findings of previous trials.

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