The Role of Recombinant Erythropoietin in Childhood Cancer

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Key Words. Recombinant erythropoietin • Cancer-associated anemia • Children • Childhood cancer

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LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Describe the pathophysiology of anemia in children with cancer and explain the rationale for the use of rHuEPO in the prevention and treatment of cancer-associated anemia.
2. Discuss the current indications for the use of rHuEPO in childhood cancer.
3. Explain how the use of rHuEPO in patients with cancer may result in tumor progression and inferior survival outcome.

ABSTRACT

Anemia in children with cancer is not an uncommon complication and is usually multifactorial in etiology. In numerous trials in adult cancer patients, treatment with recombinant erythropoietin has been shown to increase hemoglobin levels, reduce red blood cell transfusion requirements, and improve quality of life. Much less has been published of its use in the prevention or treatment of cancer-associated anemia (CAA) in children, in whom chemotherapy is usually more intensive and likely to result in greater myelosuppression. This review critically evaluates the published evidence of its use in childhood cancer especially; its safety and efficacy in the prevention and treatment of CAA and some indications for its use in childhood cancer are suggested. The Oncologist 2008;13:157–166

INTRODUCTION

Anemia in children with cancer is a significant problem that not only affects the patient’s quality of life (QoL) but also may have an adverse impact on treatment response. Although red blood cell (RBC) transfusions are very effective in ameliorating the symptoms of anemia, their use can lead to undesirable side effects, principally transfusion-associated infections (cytomegalovirus, HIV, hepatitis B and C), allo-sensitization, immune suppression, and iron overload, any of which may adversely affect treatment outcome. Moreover, as RBC transfusions only have a temporary effect on hemoglobin (Hb) levels, it is important to identify alternative strategies of anemia correction that avoid or minimize the need for such transfusions.

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Replacement therapy with recombinant human erythropoietin (rHuEPO) is a rational approach for the treatment of cancer-associated anemia (CAA). The recombinant product has the same amino acid composition as the natural human EPO and an almost identical carbohydrate structure [1, 2], and therefore, antibodies against rHuEPO are most unusual. Numerous studies in adult cancer patients have shown that treatment with rHuEPO hastens erythropoietic recovery and reduces RBC transfusion requirements [3–8]. Much less has been published of its use as an alternative to RBC transfusions in the treatment or prevention of CAA in children, in whom chemotherapy is usually more intensive and likely to result in greater myelosuppression. A physiologic rationale for the use of rHuEPO in children undergoing myelosuppressive chemotherapy is the observation that these patients have a blunted EPO response to anemia, and it is therefore possible that this relative insensitivity to physiological levels of EPO could be overcome with rHuEPO [9].

This report reviews the pathophysiology of CAA in children and critically examines the published data regarding the safety, feasibility, and efficacy of rHuEPO in the prevention and treatment of CAA in children.

PATHOPHYSIOLOGY OF ANEMIA IN CHILDREN WITH CANCER

The pathogenesis of CAA is multifactorial, and some of the factors responsible for anemia in adults are also directly causal for CAA in children. The important contributory factors include: (a) bone marrow suppression, (b) defective/decreased erythropoiesis, (c) decreased production of EPO, and blood loss.

Bone Marrow Suppression

Suppression of hematopoiesis resulting from bone marrow infiltration is the primary cause of anemia in malignant disorders such as neuroblastoma, leukemia, and non-Hodgkin’s lymphoma. Chemotherapy and or radiotherapy can also impair erythropoiesis as a result of a direct myelotoxic effect on the bone marrow RBC progenitors.

Defective/Decreased Erythropoiesis

Defective erythroid progenitor activity secondary to the presence of soluble inhibitory factors associated with cancer has been postulated as causative for CAA in children [10, 11]. Furthermore, increased circulating levels of cytokines in blood, such as interleukin 1, tumor necrosis factor α, and transforming growth factor β, have been shown in both hematological and solid tumor malignancies in adults [12–15]. These cytokines not only have a direct inhibitory effect on erythropoiesis but also cause a blunting in the sensitivity of the erythroid progenitors to endogenous EPO. Whether these findings also apply to children is not clear.

Decreased Production of EPO

Decreased EPO production by the renal tubular cells is a significant cause of CAA in patients receiving nephrotoxic chemotherapy, such as cisplatin for children with solid tumor malignancies. For reasons that are as yet unclear, EPO production in some patients with cancer is inadequate relative to the degree of anemia, and this is unrelated to renal impairment [16, 17].

Blood Loss

Although CAA is mostly a result of the disease itself, other causes include external blood loss resulting from thrombocytopenia, usually from the gastrointestinal tract, bleeding into a necrotic tumor, especially on commencement of treatment, and repetitive blood loss from blood sampling for routine laboratory investigations. Hemolysis resulting from mechanical factors or an antibody-mediated effect is not a significant cause of anemia in children with cancer.

ERYTHROPOIETIC AGENTS

There are currently three recombinant erythropoietic agents that are approved for use in the treatment of CAA: epoetin alfa, epoetin beta, and darbepoetin alfa. Epoetin alfa and epoetin beta are recombinant preparations of endogenous EPO, whereas darbepoetin alfa is a synthetic longer-acting analogue of epoetin alfa. Structurally, darbepoetin alfa differs from rHuEPO (epoetin alfa and epoetin beta) in containing 5 N-linked oligosaccharide chains, compared with three chains in rHuEPO [18]. The additional carbohydrate chains provide darbepoetin alfa with more glycosylation sites, which account for its longer half-life (two- to threefold longer circulating half-life when administered i.v. or s.c.) and also its fourfold lower binding affinity for EPO receptors than either epoetin alfa or epoetin beta [19–21].

Pharmacokinetics

The pharmacokinetic profiles of epoetin alfa and darbepoetin alfa in children and adolescents appear to be comparable with those of adults [22, 23]. The elimination half-life after i.v. administration is approximately 20% longer in patients with chronic renal failure than in healthy subjects. Compared with epoetin beta, epoetin alfa has a smaller volume of distribution and shorter elimination time after i.v. administration and longer absorption after s.c. administration [19]. The terminal half-life of darbepoetin alfa is approximately two- to fourfold longer than that of epoetin alfa when administered i.v. [22]. Despite the differences in their respective pharmacokinetic profiles, it is likely that the
CAAs in children. Most are small, single-center studies and difficult to interpret or validate the therapeutic value of EPO, agent itself [24, 25].

**Clinical Efficacy**

Despite the results obtained with rHuEPO in the treatment of CAA in adults, there is only a handful of randomized studies using rHuEPO in the treatment or prevention of CAA in children. Most are small, single-center studies and differ in their trial design, in the variable enrollment of patients with solid or hematological malignancies, in nonconformity in drug dosages and dosing schedule, and with some studies combining rHuEPO with G-CSF, rendering it difficult to interpret or validate the therapeutic value of EPO in the treatment or prevention of CAA in children. Table 1 summarizes the results of all the randomized studies in which rHuEPO has been used in the prevention and/or treatment of CAA in children.

Table 1. Randomized studies in which rHuEPO has been used in the prevention and/or treatment of CAA in children

<table>
<thead>
<tr>
<th>Trial</th>
<th>Study design</th>
<th>Type of malignancy</th>
<th>Dose and schedule of EPO</th>
<th>Mean Hb/HCT change baseline—final</th>
<th>RBC transfusions</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bennetts et al. (1995) [26]</td>
<td>Randomized</td>
<td>ALL</td>
<td>Epoetin alfa, 150 U/kg thrice weekly i.v./s.c.</td>
<td>Not reported</td>
<td>Lower volume of RBC transfusions for children with low-risk ALL randomized to EPO (36.8 ± 12.7 ml versus 69.5 ± 36.1 ml)</td>
<td>No difference in volume or number of RBC transfusions overall between the 2 groups; however, in low-risk ALL patients, EPO treatment significantly reduced volume of RBC transfusions (p &lt; .02)</td>
</tr>
<tr>
<td>Czaki et al. (1998) [27]</td>
<td>Randomized</td>
<td>NBL, ES, OS, STS</td>
<td>Epoetin beta, 150 U/kg s.c. thrice weekly</td>
<td>EPO, 39.3%; control, 33.2%; p &lt; .05</td>
<td>Trend toward fewer RBC transfusions during third month</td>
<td>Greater response rate (Hb &gt; 2 g/dl by wk 12) in the EPO group (48% versus 17%; p &lt; .05); trend toward better performance status in the EPO group</td>
</tr>
<tr>
<td>Porter et al. (1996) [28]</td>
<td>Randomized</td>
<td>RMS, OS, ES, US</td>
<td>Epoetin alfa, 150 U/kg thrice weekly i.v./s.c.</td>
<td>Not reported</td>
<td>EPO, mean of 4.5 units transfused; placebo, mean of 13 units transfused</td>
<td>EPO treatment significantly reduced RBC (p = .01) and platelet (p = .005) transfusions</td>
</tr>
<tr>
<td>Ragni et al. (1998) [29]</td>
<td>Randomized</td>
<td>Various solid tumors (22 courses of chemotherapy)</td>
<td>Epoetin alfa, 150 U/kg thrice weekly s.c.</td>
<td>Mean Hb nadir: EPO, 10.36 g/dl; control, 8.7 g/dl (p &lt; .05)</td>
<td>EPO, 2; control, 27</td>
<td>EPO effective in reducing RBC and platelet transfusions (18% versus 70%; p &lt; .05)</td>
</tr>
<tr>
<td>Bykpmakuçu et al. (2002) [30]</td>
<td>Randomized</td>
<td>Various solid tumors including lymphomas</td>
<td>Epoetin alfa, 150 U/kg thrice weekly s.c.</td>
<td>EPO, +1.71 g/dl; control, +0.07 g/dl (p = .027)</td>
<td>EPO, 1; control, 8</td>
<td>EPO effective in reducing RBC transfusions (p = .008)</td>
</tr>
<tr>
<td>Henze et al. (2002) [31]</td>
<td>Randomized</td>
<td>Various solid tumors and ALL</td>
<td>Epoetin alfa, 600–900 U/kg once weekly</td>
<td>Not reported</td>
<td>Reduction in RBC transfusions for children with ALL; EPO, 66% versus control, 89% (p = .02)</td>
<td>EPO effective in reducing RBC transfusions for ALL patients; no difference in transfusion requirements for non-ALL patients (p = .65)</td>
</tr>
<tr>
<td>Wagner et al. (2004) [32]</td>
<td>Randomized</td>
<td>High risk NBL</td>
<td>Epoetin alfa, 200 U/kg per day; G-CSF, 10 μg/kg per day; both s.c.</td>
<td>G-CSF, +0.8 g/dl; G-CSF + EPO, +0.1 g/dl (p = .55)</td>
<td>G-CSF, 207; G-CSF + EPO, 258</td>
<td>Addition of EPO to G-CSF did not reduce transfusion requirements in patients with high-risk NBL</td>
</tr>
<tr>
<td>Razzouk et al. (2006) [33]</td>
<td>Randomized</td>
<td>Nonmyeloid malignancy, excluding brain tumors</td>
<td>Epoetin alfa, 600–900 U/kg once weekly i.v.</td>
<td>EPO, +1.3 g/dl; control, +1 g/dl (p = 1.29)</td>
<td>After 4 wks, more EPO patients than control patients were transfusion free (38.7% versus 22.5%; p = .01)</td>
<td>Greater response rate (Hb &gt; 2 g/dl) in the EPO group (56.5% versus 34.9%; p = .002); QoL significantly better in the EPO group among children 5–7 yrs of age (88% versus 78.1%; p = .043)</td>
</tr>
<tr>
<td>Abdelrazik and Fouda (2007) [34]</td>
<td>Randomized</td>
<td>ALL</td>
<td>Epoetin alfa, 450 U/kg once weekly s.c.</td>
<td>EPO, 3.08 ± 1.48 g/dl (p &lt; .001); increase in Hb &gt; 2 g/dl seen in 70% of patients in the EPO group</td>
<td>Not reported</td>
<td>The overall response rate (Hb increase &gt; 2 g/dl or Hb &gt; 12 g/dl) was 90% for patients randomized to receive EPO; EPO treatment significantly improved overall QoL (p &lt; .001)</td>
</tr>
</tbody>
</table>

Abbreviations: ALL, acute lymphoblastic leukemia; CAA, cancer-associated anemia; EPO, erythropoietin; ES, Ewing’s sarcoma; Hb, hemoglobin; HCT, hematocrit; NBL, neuroblastoma; OS, osteosarcoma; rHuEPO, recombinant human erythropoietin; QoL, quality of life; RMS, rhabdomyosarcoma; STS, soft tissue sarcoma; US, undifferentiated sarcoma.
QUESTIONS ADDRESSED BY THIS REVIEW
1. Can rHuEPO be used prophylactically to prevent anemia?
2. Does treatment with rHuEPO have a positive impact on Hb levels?
3. Is rHuEPO treatment effective in reducing packed RBC transfusions?
4. Does treatment with rHuEPO improve survival outcome?
5. Are the side effects of rHuEPO tolerable in children?
6. Does rHuEPO treatment improve QoL in children with cancer?

REVIEW OF EVIDENCE
The review of evidence on which this report is based consists largely of a review of published studies on the use of rHuEPO in childhood cancer. Admissible data included controlled, randomized trials that compared treatment outcomes in preventing or treating anemia with and without the use of rHuEPO. Studies were included if (a) the population consisted of children (as defined by the individual study), (b) there was randomization between rHuEPO and placebo or no therapy, (c) rHuEPO was administered after commencement of chemotherapy, before the development of anemia, and (d) identical chemotherapy immediately preceded rHuEPO and placebo administration or no therapy. Study exclusion criteria were (a) a study population that consisted of adults and (b) nonrandomized rHuEPO allocation.

EPOETIN ALFA AND BETA—RANDOMIZED STUDIES

Study 1
In this multicenter, prospective study [26], 37 patients with newly diagnosed acute lymphoblastic leukemia (ALL) were randomized either to receive rHuEPO (EPO group; n = 19) or to a control group (no EPO group; n = 18). Patients randomized to the EPO group received epoetin alfa at a dose of 150 U/kg three times a week i.v. or s.c. during the remission induction, consolidation, and delayed intensification phases of treatment. RBC transfusions were recommended for all patients when their Hb dropped below 7.5 g/dl. The distribution of low-risk and intermediate-risk ALL patients was equal between the two randomized groups. Although, overall, there was no significant difference in the volume or number of RBC transfusions between the two groups of patients, low-risk ALL patients randomized to receive rHuEPO required a significantly lower volume of RBC transfusions than patients in the control group (16.8 ± 12.7 ml versus 69.5 ± 36.1 ml; p = .02). The use of rHuEPO was not associated with any significant toxicity. The study concluded that the administration of rHuEPO at a dose of 150 U/kg three times a week was safe in children with ALL and mostly benefited children with low-risk disease.

Study 2
This was a single-center, open-label, prospective, randomized study [27]. Twenty (aged 4–18 years) patients with solid tumor malignancies undergoing cyclical chemotherapy treatment were randomized either to receive rHuEPO (EPO group; n = 12) or to the control group (no EPO group; n = 8). rHuEPO recipients also received supplemental iron for the duration of the study. Patients randomized to the EPO group received rHuEPO at a dose of 150 IU/kg s.c. three times per week for a minimum of 12 weeks or three cycles of chemotherapy. However, of the 20 enrolled patients, only 15 (EPO group, 8; no EPO group, 7) were evaluable for the efficacy analysis while 18 were eligible for the safety analysis. Patients in the EPO group had significantly greater hematocrit values (39.3% ± 4.2% versus 33.2% ± 2.1%; p < .05) and progressively higher Hb levels (13.11 ± 1.13 g/dl versus 11.06 ± 1.35 g/dl; p < .05) than patients in the no EPO group. Although total transfusion requirements were not significantly different in the two groups during the entire study period, nonetheless, no patient in the EPO group required RBC transfusions in the third month of treatment, compared with four in the no EPO group. In addition, there was a generally better performance status for patients in the EPO group, with weight loss being lower in the EPO group than in the no EPO group (0.7 kg versus 2.5 kg). No significant adverse effects were reported after rHuEPO administration.

Study 3
A placebo-controlled, randomized study that evaluated the effect of epoetin alfa along with iron supplementation on transfusion requirements in children with sarcomas receiving intensive chemotherapy concluded that prophylactic rHuEPO significantly reduced RBC transfusion requirements [28]. In this study, although 24 children were randomized, only 20 patients were deemed evaluable. Of these 20 children, 10 each were randomly assigned to receive either epoetin alfa or a matching volume of placebo (normal saline) for 16 weeks. The dose of rHuEPO was 150 IU/kg three times per week s.c. or i.v. Compared with placebo, children randomized to receive epoetin alfa had significantly fewer RBC (p = .02) and platelet (p = .005) transfusions. However, there was no difference in the number of patients who required any RBC transfusion in the study (EPO group, 9/10; no EPO group, 10/10). No significant toxic effects of rHuEPO were reported.
Study 4
In this single-center, randomized study [29], children with cancer undergoing cyclical chemotherapy treatment were randomized either to receive rHuEPO (EPO group) or to the control group (no EPO group). rHuEPO recipients also received supplemental iron for the duration of the study. Patients randomized to the EPO group received epoetin alfa at a dose of 150 IU/kg s.c. three times a week for 16 weeks. Epoetin alfa was commenced after a mean of 4.7 courses of chemotherapy (range, 1–14). Patients in the EPO group had a significantly lower rate of RBC and platelet transfusion (18%) than patients in the control group (45%) (p < .05). The mean nadir Hb during 22 courses of chemotherapy in the EPO group was 10.6 g/dl (range, 7.7–13.8 g/dl), compared with 8.7 g/dl (range, 5.5–13.5 g/dl) during 36 courses of chemotherapy in the no EPO group (p < .05). No adverse effects were reported after rHuEPO administration. It was concluded that rHuEPO reduced RBC transfusion requirements and was effective in preventing CAA in children undergoing cyclical chemotherapy.

Study 5
In a controlled, prospective, randomized, single-center study [30], 34 patients with solid tumors were randomized to receive either epoetin alfa s.c. at a dose of 150 IU/kg (n = 17) three times a week for 8 weeks or a nonplacebo standard care (no EPO group; n = 17). No patient received iron supplementation during the study. Just over half of the patients received a nonplatinum-based chemotherapy regimen while approximately 40% also received radiotherapy. Serum EPO levels were measured in all patients at study entry, and again at the end of the study in patients who were randomized to receive epoetin alfa. Outcome endpoints were the total number of packed RBC transfusions and tolerability of epoetin alfa.

Although there was no significant difference in the EPO levels between the two groups of patients at study entry, the median EPO level was lower at the end of the study (3.5–270 IU/l; median, 22 IU/l) than at study entry (14–410 IU/l; median, 80 IU/l) in the epoetin alfa group. Compared with the control group, patients randomized to receive epoetin alfa had a significantly higher Hb level at the end of the study (p = .027) and also significantly fewer RBC transfusions over the course of the study (p = .008). Except for one patient who developed hypertension, no adverse effects were reported in any of the remaining 16 patients randomized to epoetin alfa.

Study 6
This randomized, controlled trial [31] evaluated the effect of once-weekly epoetin alfa (600 or 900 IU/kg) for 20 weeks on reducing RBC transfusion requirements in newly diagnosed children with cancer. Of the 232 children enrolled in the study, 37% had ALL. In this trial, all enrolled patients were randomized either to receive rHuEPO (EPO group) or to the non rHuEPO control group (no EPO group). The primary outcome measure was the RBC transfusion rate after 4 weeks until the end of the study. Secondary endpoints included days to first transfusion after 4 weeks, increase in Hb level from baseline, number of RBC units transfused, and number of transfusion episodes. All patients randomized to receive rHuEPO had a significantly lower number of RBC units transfused as well as fewer transfusion episodes than patients in the no EPO group (66% versus 89%; p = .02). No such differences were noted between the EPO group and the no EPO group in the set of non-ALL patients (56% versus 60%; p = .65). Furthermore, significant differences were seen for most of the secondary endpoints for children with ALL. There was no greater incidence of thrombotic vascular events in patients randomized to receive rHuEPO. The study concluded that, while there was no significant difference overall in the transfusion incidence between the EPO and the no EPO groups, once-weekly epoetin alfa reduced RBC transfusion requirements among children with ALL.

Study 7
A recent single-center, randomized study that combined prophylactic rHuEPO with G-CSF in high-risk neuroblastoma patients in an effort to reduce RBC transfusion requirements concluded that the addition of rHuEPO provided no added benefit for these patients [32]. Thirty-eight children with metastatic neuroblastoma were randomized to receive either G-CSF alone (n = 20) or a combination of G-CSF and rHuEPO (n = 18) during the course of six cycles of induction chemotherapy. Induction chemotherapy comprised three cycles of cyclophosphamide, doxorubicin, and etoposide alternating with three cycles of cisplatin and etoposide. The dose of rHuEPO was 200 IU/kg per day s.c., which commenced 24 hours after completion of a chemotherapy cycle and was continued until 2 days before the start of the next cycle. rHuEPO was administered daily if the Hb level was <10 g/dl but thrice a week if the Hb concentration was >10 g/dl. Because the aim was to maintain Hb between 10 and 13 g/dl, rHuEPO was discontinued when the Hb was >13 g/dl and recommenced when it fell to <13 g/dl. Interestingly, patients receiving rHuEPO had a lower average Hb concentration during five of the six cycles, and in fact, also received more RBC transfusions (258 versus 207) than patients in the G-CSF alone group. The median number of RBC transfusions given during induction when the Hb level was ≤8 g/dl was

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higher for patients receiving G-CSF plus rHuEPO (10; range, 2–16) than for patients in the G-CSF alone group (8; range, 3–16) (p = .04) The median decrease in Hb concentration at the end of the study (difference between the Hb concentration at the start of the study and the study end) was 0.8 g/dl for those who received G-CSF alone compared with 0.1 g/dl for those given G-CSF and rHuEPO (p = .35). No significant toxic effects of rHuEPO were reported. There were no differences in the probability of survival or progression-free survival between the two groups.

**Study 8**

In a more recently published, double-blind, placebo-controlled, multicenter trial [33], 224 anemic children with nonmyeloid hematological and solid tumor malignancies (excluding brain tumors) received either rHuEPO (n = 113), 600–900 IU/kg, or placebo (n = 111) once weekly i.v. for 16 weeks. Iron supplementation was recommended if transferrin saturation dropped to <20% or if serum ferritin was <100 ng/ml. Outcome measures included health-related QoL (HRQoL) generic scale (GS) and cancer-specific scale (CS) scores, tolerability of rHuEPO, and RBC transfusion requirements. Hb changes were determined by the repeated measures analysis method on data from baseline. Although the mean change in Hb from baseline was not significantly different between the EPO and the placebo groups (1.3 g versus 1.0 g; p = .129), patients in the rHuEPO group had a significantly greater increase in Hb than patients in the placebo group (p = .002) and were more likely to be transfusion free after 4 weeks of treatment (38.7% versus 22.5%; p = .01). Although the mean final values for total GS score and CS domain score were not significantly different between the two groups (p = .763; p ≥ .238), a significant positive correlation was seen between Hb change and HRQoL among children 5–7 years of age in the rHuEPO group (p = .043). Although serious adverse event rates were similar in the two groups of patients (EPO group, 68.8%; placebo group, 74.5%), the rate of reported infections was lower in the EPO group (6.3% versus 12.7%). Conversely, the rate of clinically relevant thrombovascular events was higher in the EPO group (n = 6; 5.4%) than in the placebo group (n = 2; 1.8%). Three patients in the EPO group were withdrawn early from the study (central venous catheter complication, 1; cardiorespiratory arrest secondary to sepsis, 1; and grade 3 sagittal vein thrombosis, 1) compared with one patient in the placebo group (cerebral infarction). No deaths resulting from thrombotic vascular events were reported in the study.

**Study 9**

This prospective, single-center, randomized, controlled trial [34] evaluated the effect of once-weekly rHuEPO (epoetin alfa, 450 IU/kg s.c.) for 12 consecutive weeks in reducing RBC transfusion requirements and improving QoL in children with ALL in remission receiving maintenance chemotherapy. In this trial, 60 children with ALL were randomized either to receive epoetin alfa (EPO group; n = 30) or to the control group (no EPO group; n = 30). Both groups were evenly matched with regard to age, sex, baseline Hb level, remission status, leukemia risk category (low-risk and standard-risk patients), and chemotherapy treatment regimen. Thirty patients were evaluable for hematological response. For patients who were randomized to receive epoetin alfa, the mean increase in Hb value from baseline to final evaluation was 3.08 ± 1.48 g/dl (p < .001), while the overall response rate (i.e., Hb ≥12 g/dl or Hb increase of ≥2 g/dl in the absence of blood transfusion) was 90% (n = 27/30). Among the 30 patients evaluable for QoL assessment, epoetin alfa treatment was found to significantly increase the mean cancer linear analogue scale score for energy level, ability to perform daily activity, and overall QoL from baseline to the time of final evaluation. The study concluded that treatment with rHuEPO increased Hb levels, reduced the incidence of RBC transfusions, and improved functional status and QoL in patients with ALL on maintenance therapy. rHuEPO was well tolerated, and no significant adverse effects were reported.

**Perils and Side Effects of rHuEPO Use**

Published experience regarding the acute undesirable effects of rHuEPO treatment in children with cancer suggests that the toxic effects of rHuEPO are minimal [26–30, 35]. The most commonly reported adverse reactions are local erythema and swelling at the injection site. rHuEPO-associated exacerbation of hypertension, a frequently described predicament in children with renal disease, is an uncommon complication in children with cancer. No other significant constitutional symptoms associated with the use of rHuEPO have been cited in these patients. Thromboembolic events have been described in children with renal disease but are exceptionally rare [36]. There is no evidence that rHuEPO treatment has a detrimental effect on platelet count recovery.

**Association of rHuEPO Therapy with Malignancy**

Although several clinical trials on the use of rHuEPO in adults with cancer have produced persuasive results of its efficacy, nonetheless, its routine clinical use in this setting has not yet gained unanimous acceptance. This is in part re-
lated to the higher risk for thromboembolic events and related cardiovascular complications, but also is a consequence of the results from a few randomized studies that seem to suggest that patients who were randomized to receive EPO had a higher mortality rate than patients in the placebo arms [37–42]. The poor survival outcome results of these three studies have generated uncertainty on the safety of rHuEPO therapy and have led to conjecture that rHuEPO may lead to accelerated tumor growth. In three of the trials, patients randomized to receive rHuEPO were being treated to above the recommended optimum Hb level (>12 g/dl) [37, 38, 40], but the survival decrement for patients assigned to receive rHuEPO was not related to any escalated thromboembolic episodes. A rather baffling feature of the Breast Cancer Erythropoietin Survival Trial (BEST) [38] was that almost all of the excess deaths in the EPO arm occurred early, in the first 4 months of the study (i.e., 25 excess deaths in the EPO arm, 41 versus 16 in the placebo arm), when the effect of rHuEPO should have been minimal. The third trial was closed prematurely [39] when an unplanned interim safety analysis revealed a significantly poorer overall survival in the group randomized to receive rHuEPO. A worrisome aspect of this trial was the fact that all the patients in the EPO arm who died of progressive lung cancer were no longer receiving active treatment. The early closure of the Goldberg [41] trial for patients with head and neck cancer was predicated on a detrimental effect on locoregional control and a trend toward a shorter survival duration in patients randomized to receive darbepoetin alfa. The results of two unpublished trials (Anemia of Cancer Study and Lymphoid Cancers Anemia Study) also show a shorter overall survival time in patients who were randomized to receive darbepoetin alfa [42]. Collectively, these trials have cast some doubt about the safety of rHuEPO for the treatment or prevention of CAA, particularly in the highly curable childhood cancers. Although the U.S. Food and Drug Administration (FDA) has approved the use of rHuEPO in the treatment of CAA, a recent (November 2006; updated February and March 2007) FDA alert warns physicians that the use of rHuEPO to achieve a target Hb level of ≥12 g/dl shortens the time to tumor progression in patients with advanced head and neck cancer and also shortens the overall survival time in patients with metastatic breast cancer on chemotherapy. Additionally, the FDA does not recommend the use of rHuEPO in patients with active cancer not on actual chemotherapy or radiotherapy treatment.

It is possible that these unexpected adverse effects of rHuEPO on survival or tumor progression in these patients may be related to the type of erythropoietic agent used and the specific type of cancer. Some malignancies may be more sensitive to rHuEPO and to the dose and schedule of rHuEPO therapy. To date, there have been no reports of poor survival outcomes in children who have had rHuEPO treatment for CAA.

**Summary and Future Directions**

Despite the fact that rHuEPO has been shown to be effective in the treatment of CAA in adults, the potential role for this hormone in the treatment or prevention of anemia in children with cancer remains unclear. Any intervention is of clinical value if it improves overall survival or QoL and/or is cost-effective. The data from the few randomized pediatric EPO trials, although limited by the small numbers of patients enrolled, suggest that packed RBC transfusion requirements are significantly lower in children who receive rHuEPO [26, 28–31, 33, 34]. It is logical to assume that by increasing the Hb level and thereby ameliorating the symptoms of anemia, rHuEPO therapy will result in a better QoL for these children. However, in the nine controlled trials reviewed in this report, only two studies [33, 34] specifically addressed the QoL issue in these patients. In the Razzouk et al. [33] study, although there was no difference in the HRQoL between the two treatment groups overall, QoL was significantly better in the EPO group among patients 5–7 years of age (88% versus 78.1%; p = .043). In the second and more recently published study [34], treatment with rHuEPO during maintenance therapy in children with ALL was associated with a significant improvement in their performance status and QoL. One other study [27] did report an improvement in the performance status of patients randomized to rHuEPO treatment. Unless explicit measurement of QoL is a predefined objective of the trial, it is not possible to determine the effects of rHuEPO treatment (such as requirement for painful injections, need for packed RBC transfusions, increased laboratory monitoring, etc.) on patients and their families, and whether or not the advantages associated with fewer transfusions and hospitalizations are offset by these factors.

There is no evidence to suggest that the use of rHuEPO has either a positive or a negative impact on survival, although this was not a specific outcome endpoint in the majority of the trials. In the only study that had survival as an outcome measure [32], the use of rHuEPO did not affect overall or progression-free survival. rHuEPO was well tolerated in all the studies and there was no significant difference in reports of serious adverse events with thromboembolism or severe hypertension.

A serious concern is the considerable expense of rHuEPO. This review does not address the pharmacoeconomic costs of rHuEPO therapy for CAA. Actual costs were difficult to calculate because none of the trials com-
pared the cost-effectiveness of erythropoietic proteins with packed RBC transfusions with respect to QoL or overall survival. Packed RBC transfusions provide effective and rapid control of the symptoms of anemia, and although the risks of transfusion-associated infections are valid, they are very small. Therefore, any benefit with rHuEPO must be gauged in terms of improvement in QoL against the risk for potential toxicity and costs. If there is no improvement in QoL or survival, it is highly improbable that rHuEPO will be considered cost-effective for the treatment of CAA. It is therefore imperative that future prospective trials take the above parameters into account when evaluating the cost-effectiveness of rHuEPO for the treatment of CAA in children.

**IS EPO THERAPY IN CHILDREN SAFE?**
The mounting unease regarding the potential stimulation of tumor cell growth by EPO is real, because there is demonstrable evidence of the presence of EPO receptors in pediatric tumors and various cancer cell lines [43, 44]. There is evidence of EPO-mediated activation of signal transduction pathways such as mitogen-activated protein kinase and Janus kinase–signal transducer and activator of transcription in certain human cancers [45, 46]. Activation of these signaling pathways can lead to tumor progression and growth. Additionally, it has been shown that endothelial cells also express EPO receptors, and that EPO is an important angiogenic factor and tumor progression can occur as a consequence of augmented tumor angiogenesis and neoangiogenesis [47–49]. Moreover, EPO is also known to protect tumor cells by inhibiting apoptosis [50, 51]. Nonetheless, there is some uncertainty as to whether or not the antibodies used to detect EPO receptors in tumor cells are indeed EPO specific [52, 53], because some cancer cells do not show any proliferative response to EPO [54], and in fact, some cancer cells undergo greater apoptosis [55, 56] on exposure to EPO.

Given the poor survival results of some of the recent adult trials [37–42], caution is advised on the use of recombinant EPO in the treatment or prevention of CAA in children. Clearly, further research is required before definitive conclusions can be drawn on the important question of whether the use of rHuEPO is safe in preventing or treating CAA in children. Suppression of tumor angiogenesis and progression by EPO blockade may constitute a potential target for the therapeutic modulation of angiogenesis in cancer [57].

On the basis of published evidence on the risks and benefits of rHuEPO in the treatment or prevention of CAA in children and adults, the following suggestions can be made:

1. Causes of anemia other than malignancy should be ascertained (iron deficiency, blood loss, etc.) and corrected before commencement of EPO treatment.

2. Prophylactic treatment with EPO to prevent anemia is not recommended for children undergoing chemotherapy and or radiotherapy who have normal Hb levels at the start of treatment.

3. The target aim for the Hb value should be 12 g/dl, at which time the dose should be titrated to maintain that level or EPO therapy could be stopped and restarted when the level falls to <10 g/dl.

4. Recombinant EPO treatment in children undergoing chemotherapy should be commenced at an Hb level of 9–11 g/dl, dependent on symptoms of anemia. RBC transfusion is also an option, depending on the clinical severity of the anemia.

5. Once-weekly dosing of EPO is satisfactory for children, and this is also recommended by the FDA.

6. Although the optimal dosage of rHuEPO in children remains unclear, doses of 600–900 IU/kg once weekly of epoetin alfa appear to be effective. The use of higher doses cannot be recommended outside a clinical trial.

7. The use of EPO to support Hb levels in children undergoing radiotherapy cannot be recommended, because there are insufficient pediatric data to support this practice.

8. Continuing EPO treatment beyond 8 weeks in the absence of a response (rise in Hb level by 2 g/dl) does not appear to be beneficial.

It is important that the use of rHuEPO for the treatment or prevention of CAA in children is carried out within controlled, randomized clinical trials. Whether rHuEPO protein therapy will eventually replace RBC transfusions is difficult to predict. Current evidence of its efficacy is limited in children with CAA, and as with other growth factors, substantial knowledge will only accrue in the context of a clinical trial where its efficacy and benefit can be assessed accurately and objectively.

**REFERENCES**


4. Quijt I, Robeson C, Lau CY et al. Epoetin alfa therapy increases hemoglobin levels and improves quality of life in patients with cancer-related ane-


44 Batra S, Perelman N, Luck LR et al. Pediatric tumor cells express erythropoietin and a functional erythropoietin receptor that promotes angiogenesis and tumor cell survival. Lab Invest 2003;83:1477–1487.
Study 3
A placebo-controlled, randomized study that evaluated the effect of epoetin alfa along with iron supplementation on transfusion requirements in children with sarcomas receiving intensive chemotherapy concluded that prophylactic rHuEPO significantly reduced RBC transfusion requirements [28]. In this study, although 24 children were randomized, only 20 patients were deemed evaluable. Of these 20 children, 10 each were randomly assigned to receive either epoetin alfa or a matching volume of placebo (normal saline) for 16 weeks. The dose of rHuEPO was 150 IU/kg three times per week s.c. or i.v. Compared with placebo, children randomized to receive epoetin alfa had significantly fewer RBC \( p < .01 \) and platelet \( p < .005 \) transfusions. However, there was no difference in the number of patients who required any RBC transfusion in the study [EPO group, 9/10; no EPO group, 10/10]. No significant toxic effects of rHuEPO were reported.