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Original Paper

Recombinant Human Erythropoietin in the Prevention of Chemotherapy-induced Anaemia in Children with Malignant Solid Tumours

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This prospective, randomised pilot study was designed to evaluate safety, feasibility and efficacy of recombinant human erythropoietin (rhEPO) in the prevention and treatment of chemotherapy-induced anaemia in children with solid tumours. 20 children (age 4–18 years) undergoing cyclic combination chemotherapy were randomised either to a control group or to receive rhEPO at a dose of 150 U/kg/dose subcutaneously three times/week for a minimum of 12 weeks or three chemotherapy cycles. Of 15 evaluable patients, 8 were randomised to the rhEPO group and 7 to the control group. RhEPO-treated patients showed an increase in the haematocrit over the first 8 weeks of therapy, with a significantly higher mean haematocrit at week 8 (33.2 ± 2.1% versus 39.3 ± 4.2% in the control and rhEPO groups, respectively, $P < 0.05$). Similarly, significantly higher haemoglobin concentrations could be demonstrated in the rhEPO group by week 8 (11.06 ± 1.35 g/dl versus 13.11 ± 1.13 g/dl in the control and rhEPO groups, respectively, $P < 0.05$), with higher precycle haemoglobin before chemotherapy cycles 3 and 4 and higher midcycle haemoglobin between cycles 3 and 4. There was a trend towards a reduction of transfusion requirements during the 3rd month of therapy in rhEPO patients. The results of this pilot study indicate a significant benefit of rhEPO in children treated with intensive combination chemotherapy regimens. Further studies should target issues such as appropriate dosing, timing and duration of rhEPO therapy in children with cancer. © **1998 Elsevier Science Ltd. All rights reserved.**

Key words: recombinant human erythropoietin, chemotherapy-induced anaemia, children, malignant solid tumour
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INTRODUCTION

CHILDREN UNDERGOING cancer chemotherapy frequently develop anaemia, which is usually corrected by the administration of a red blood cell transfusion [1]. Transfusions place the patient at increased risk of infections (CMV, EBV, HIV, Hepatitis B, C), allergic reactions, iron overload and alloimmunisation, any of which may adversely affect treatment outcome and survival [2–4]. Given the high response and cure rates of paediatric cancer, approaches to avoid transfusions and their long-term complications seem to be especially justified in children.

Since the availability of recombinant human erythropoietin (rhEPO), several prospective, randomised studies have been completed with its use in adult patients with cancer. According to these studies, a significant rise in haemoglobin (Hb) and haematocrit (Hct) levels could be demonstrated in responding patients within 4–6 weeks of starting rhEPO administration. rhEPO dose varied between 25 and 300 U/kg/dose and, in most trials, was given subcutaneously, three times a week, with prophylactic intent parallel to chemotherapy in order to decrease the frequency of anaemia. Studies also confirmed that rhEPO treatment reduced transfusion requirements and improved daily activity levels and overall quality of life of cancer patients. Side-effects of rhEPO therapy were usually mild and included hypertension, flushes, headaches and a few rare episodes of deep venous thrombosis [5–7].

In spite of the excellent results obtained with rhEPO in adult cancer patients, so far there have been no randomised

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studies reported using rhEPO in the treatment of cancer-associated anaemia *in children*. The aim of this prospective, randomised pilot study was to evaluate safety, feasibility and efficacy of rhEPO in the prevention and treatment of chemotherapy-induced anaemia in children with solid tumours.

PATIENTS AND METHODS

Study design

The study was designed as an open-label, single institution, prospective randomised phase II clinical trial. The study protocol was approved by the ethics committee of Semmelweis Medical School, Budapest.

Patients

Children aged between 4 and 18 years with histologically proven solid tumours, such as Ewing's sarcoma, soft tissue sarcoma, osteogenic sarcoma and neuroblastoma, undergoing cyclic combination chemotherapy were eligible for the study if they had Hb values < 12 g/dl before first rhEPO administration, at least three following chemotherapy cycles could be expected. All patients had a performance status < 3 on the WHO scale and an anticipated life expectancy of > 3 months. Written informed consent had to be given by the parent or patient. Patients were excluded from the study in the presence of therapy-resistant hypertension, thrombocytosis $> 500 \times 10^9/1$, uncorrectable iron deficiency, chronic bleeding, renal insufficiency, symptomatic brain metastases, severe coagulation disorder, administration of any unregistered drug within 30 days preceding study entry and protocol non-compliance. Eligible patients were randomised centrally by an independent study monitor.

Methods

In patients randomised to the rhEPO group, rhEPO administration was started concomitantly with the next chemotherapy cycle. Three different chemotherapy protocols were used in the present study, defined by the type of malignancy and including the following drugs: vincristine, cisplatin, doxorubicin, actinomycin, methotrexate, ifosfamide and VP-16. Chemotherapy cycles were administered in 3–4 weekly intervals, according to protocol, after having reached complete haematological recovery from the previous cycle (absolute neutrophil count (ANC) $> 1.0 \times 10^9/1$, platelet count $> 150 \times 10^9/1$).

Patients received rhEPO (Recormon; Boehringer Mannheim, Mannheim, Germany) at a dose of 150 U/kg subcutaneously three times per week throughout the study, for at least 12 weeks or three chemotherapy cycles. After an initial training period, rhEPO was administered by a parent or by the patient him/herself. Iron supplementation was provided to all rhEPO-treated patients (ferrous sulphate 50–300 mg/day orally depending on body weight) for the duration of the rhEPO therapy. The rhEPO dose was kept constant during the study period, but, in the case of Hb levels exceeding 14 g/dl repeatedly, it could be withdrawn and if the Hb level was lower than 11 g/dl, the individual dose could be increased by 50 U/kg/dose. Individual Hb concentrations were aimed to be kept between 11 and 13 g/dl. Transfusions were given (10 ml/kg packed red blood cells) whenever the Hb concentration fell below 8 g/dl or at any Hb level if symptoms of hypoxia presented. The patients were seen weekly and physical examinations, measurements of blood pressure, body weight, Hb, Hct, complete blood counts including red blood cell, white blood cell and platelet counts, were performed every week. Laboratory parameters, such as serum iron, transferrin, ferritin levels, electrolytes, (LDH) lactate dehydrogenase, renal and liver function tests, were performed monthly, before each subsequent chemotherapy cycle. Side-effects, adverse events and transfusion requirements were recorded during the whole study period. An overall assessment of quality of life was also performed.

Statistical analysis

The results are expressed as means (± standard deviation) except where noted. Dichotomous variables (e.g. numbers of patients who responded) were analysed by Fisher's exact test. Exact Wilcoxon rank sum tests were used to compare the number of transfused blood units per patient given during the entire trial phase and according to different months. Unpaired Student's *t*-test was used to test for the equality of mean values of continuous variables at various study visits. Two-sided tests were used exclusively with a comparison-wise significance level of 0.05.

RESULTS

Study population

Of the 20 patients enrolled, 12 were randomised to receive rhEPO and 8 were randomised to the control group. 2 patients in the rhEPO group and 1 patient in the control group were withdrawn because of patient refusal. Two additional rhEPO patients completed three chemotherapy cycles on the study, were analysed for safety, but had to be excluded from efficacy analysis. The first patient developed uncontrollable, prolonged vaginal bleeding due to severe chemotherapy-related thrombocytopenia; the second was unable to take iron supplements. All patients except one rhEPO patient, who withdrew without ever having started rhEPO therapy, and the withdrawn control patient, were analysed for safety ($n = 18$). 8 rhEPO-treated and 7 control patients were evaluable for efficacy analysis ($n = 15$). Patients evaluated for efficacy had completed an average of 3.8 ± 3.7 (range 1–12) chemotherapy cycles before study entry in the rhEPO group and 3.9 ± 1.5 (range 1–5) cycles in the control group; had received an average of 1.4 ± 1.4 transfusions in the rhEPO group and 2.7 ± 3.0 transfusions in the control group before entering the study; and had remained on the study for 3.3 ± 0.5 versus 3.1 ± 0.4 more cycles in the rhEPO and control groups, respectively. These differences between the two groups were statistically not significant. The mean duration of rhEPO therapy was 12 ± 1 weeks.

Comparison of Hb and Hct values

A comparison of weekly mean Hb values showed higher Hb levels in the rhEPO group compared with the control group after the 4th week of therapy (Figure 1a). However, this difference became statistically significant only at week 8 (11.06 ± 1.35 g/dl versus 13.11 ± 1.13 g/dl in the control and rhEPO groups, respectively, $P < 0.05$). Mean Hct values increased progressively in the rhEPO-treated group over the first 8 weeks of therapy (Figure 1b). A comparison of mean Hct values showed significantly higher levels at week 8 in the rhEPO group (33.2 ± 2.1% versus 39.3 ± 4.2% in the control and rhEPO groups, respectively, $P < 0.05$).

Mean precycle Hb values, measured before initiation of each subsequent chemotherapy cycle, when complete haematological recovery from the myelotoxic effects of the previous

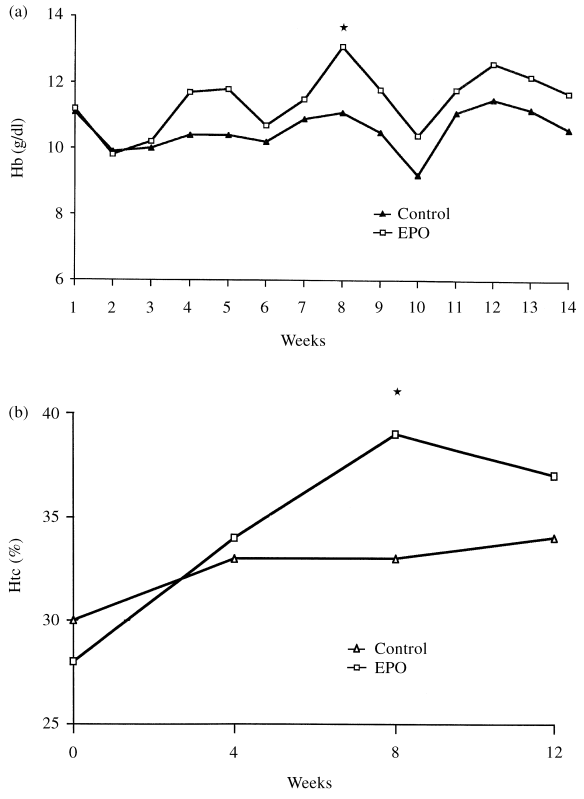

Figure 1. Changes of (a) weekly mean haemoglobin values and (b) monthly haematocrit values during the trial period in control and rhEPO-treated groups. *$P < 0.05$.

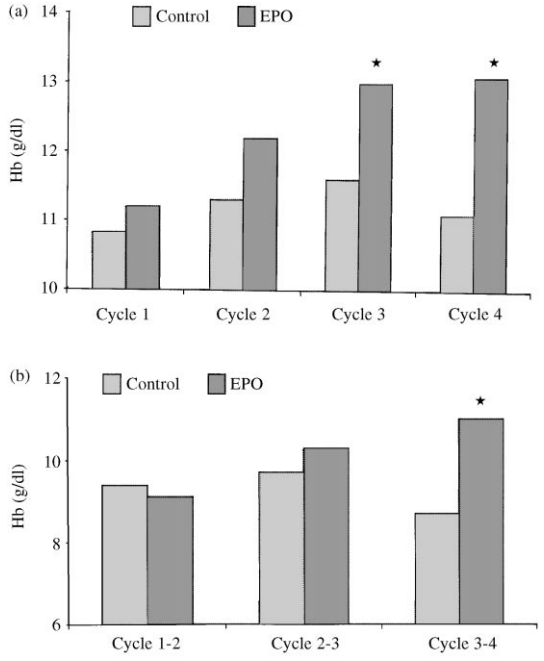

Figure 2. Comparison of (a) precycle mean haemoglobin values measured before the start of chemotherapy cycles 1–4, and (b) lowest mean midcycle haemoglobin values measured as haemoglobin nadir values between chemotherapy cycles 1 and 4, in control and rhEPO-treated groups. *$P < 0.05$.

chemotherapy cycle had been reached, differed significantly before chemotherapy cycle 3 (11.59 ± 1.21 g/dl versus 13.01 ± 1.34 gd/l in the control and rhEPO groups, respectively, $P < 0.05$) and cycle 4 (11.07 ± 1.06 g/dl versus 13.04 ± 1.74 gd/l in the control and rhEPO groups, respectively, $P < 0.05$), with higher levels in rhEPO-treated patients (Figure 2(a)). A comparison of mean midcycle Hb values showed significantly lower Hb nadirs in the control group between chemotherapy cycles 3 and 4 (8.73 ± 1.92 g/dl in the control group, 11.00 ± 1.16 g/dl in the rhEPO group, $P = 0.05$) (Figure 2b).

Response to rhEPO

Response was defined as an increase of the patients' initial Hb level by 1 g/dl by week 4 or by 2 g/dl by week 12, unrelated to the administration of a transfusion within the preceding 4 weeks. 2 of the 8 rhEPO patients responded to rhEPO treatment by week 4, but the response rate increased to 6 of 8 patients by week 12. In the control group, 1 of 7 patients showed a spontaneous response (increase in Hb by ≥ 2 g/dl) by week 12. The response rate was significantly higher in the rhEPO group compared with the control group by week 12 (6/8 rhEPO patients versus 1/7 control patients, $P < 0.05$).

Actual rhEPO doses ranged between 123 and 230 U/kg, with an average dose of 161 U/kg/patient, median 155 U/kg/patient, according to minor dose modifications allowed by the study protocol.

Transfusion requirements

Transfusion requirements were not significantly different in the two groups, when comparing the number of red blood cell units transfused over the entire course of observation, with one unit of transfusion corresponding to 200 ml of packed red blood cells. 3 of 7 control patients received 7 transfusion units over 22 chemotherapy cycles, 4 of 8 rhEPO patients received 6 transfusion units over 26 cycles (NS), corresponding to an average of 1.00 ± 1.53 units of red blood cells/control patient and 0.75 ± 0.89 units of red blood cells/rhEPO patient (NS).

Stratifying transfusion data by month of therapy, transfusion requirements were substantially reduced in the third month in rhEPO-treated patients compared with control patients (four transfusions in the control group versus no transfusions in the rhEPO group, corresponding to 0.57 units of red blood cells/patient in the control group versus 0.00 units/patient in the rhEPO group, NS).

Iron status

Serum iron and serum ferritin values were lower in the rhEPO group during the entire study period in spite of continuous iron supplementation in rhEPO patients and no iron supplementation in control patients. The differences in pre-study serum iron levels were statistically significant (20.40 ± 11.35 μmol/l in the control group, 8.95 ± 4.40 μmol/l in the rhEPO group, $P < 0.05$) but no signs of iron storage depletion could be demonstrated, as based on serum transferrin, ferritin determinations and calculations of transferrin saturation in both groups.

Performance status

In the group treated with rhEPO, a trend was seen towards an increased general performance status. Significant weight loss in cancer patients is considered to be a sign of deterioration. All control patients experienced weight loss during the observation period of 3 months with a mean decrease of body

weight of 2.5 kg (range: −5.8 + 0.0 kg). In the rhEPO group, the mean decrease in body weight was 0.7 kg (range: −5.0 to + 1.5 kg) and 4 of 8 rhEPO patients actually gained weight during the treatment period.

Adverse events

Two side-effects were reported as possibly related to rhEPO administration: the development of local erythema at the injection site followed by a generalised skin rash in one patient, and local swelling at the injection site in another patient. These events resolved after topical and systemic antihistamine therapy, never occurred repeatedly in the same patient and did not require discontinuation of rhEPO administration. No significant changes in blood pressure due to rhEPO administration could be observed in any of the patients enrolled in the trial. Treatment with rhEPO had no significant effect on platelet counts measured monthly before subsequent chemotherapy cycles (data not shown).

DISCUSSION

The results of this prospective, randomised, pilot study indicate significant benefits from rhEPO administered subcutaneously three times weekly at a dose of 150 U/kg on Hb and Hct values in a paediatric population treated with intensive combination chemotherapy regimens for different solid tumours.

In contrast to adult studies [8–10], we found that beneficial effects of rhEPO became evident only after a delay of 6–8 weeks and transfusion needs seemed to be reduced only in the third month of rhEPO application. The response rate increased in our rhEPO-treated patients from 25% at 4 weeks to 75% at 12 weeks of therapy, indicating the late type of response encountered in our patients. A possible explanation for the slower response might be the fact that our patients were pretreated with highly myelosuppressive agents and thus already exhibited some degree of cumulative bone marrow toxicity at the point of entering the study. It might also relate to differences in the response pattern between adults and children.

Our results are in contrast to the only paediatric study reported by Nenadov Beck and Beck, showing that rhEPO was safe but ineffective in the treatment of chemotherapy-induced anaemia in 15 paediatric cancer patients [11]. In our opinion, the ineffectiveness of rhEPO in the above mentioned study could be attributed to problems in study design. They chose to administer rhEPO to patients already exhibiting severe chemotherapy-induced anaemia (Hb < 7.5 g/dl), for a short period of 2 weeks, in order to ameliorate anaemia without a transfusion. In our opinion, especially in patients pretreated with chemotherapy, the preventive approach of administering rhEPO, starting it before the development of severe anaemia and giving it for a prolonged period of time, seems to be more appropriate, considering the lag-period in effect of at least 4–6 weeks.

The only side-effects attributable to rhEPO were local erythema and swelling at the injection site and a skin rash. We found no episodes of hypertension, seizures or venous thrombosis, as reported occasionally in adult cancer trials. Self administration of rhEPO by patient or parent seemed to be feasible in children of various age groups. All evaluated patients were alive at study completion and no tumour progression was observed in the study period of 3 months.

The presence of rhEPO receptors has been demonstrated on megakaryocytes and rhEPO has been shown to stimulate growth of megakaryocytic progenitor cells *in vitro* [12]. In our study, we could not demonstrate any effect of rhEPO on platelet counts measured after bone marrow recovery from the previous chemotherapy cycle, but our study design did not include a comparison of platelet nadirs or platelet recovery time.

Our observation of improvements in the performance status of rhEPO-treated patients is based on individual case histories and warrants further studies. The observed increases in body weight were considered to be a beneficial side-effect, described also in children with renal failure undergoing rhEPO treatment [13].

Our results, based on a limited number of patients, provide the first evidence that rhEPO application could be extended to the treatment of children with malignant diseases. Further studies involving larger numbers of patients seem to be warranted in order to confirm the efficacy of rhEPO therapy. Future studies should also address issues such as rhEPO dosing, adequate iron supplementation, platelet recovery and quality of life in children. Subgroups of paediatric cancer patients, defined by type of malignancy, intensity of chemotherapy, etc. most likely to benefit from rhEPO therapy should also be identified in larger trials.

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