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A multicenter study of recombinant human erythropoietin (epoetin α) in the management of anemia in cancer patients receiving chemotherapy

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Current evidence suggests that epoetin α administration is well tolerated and effective in the management of anemia of cancer and cancer chemotherapy. An open-label, multinational, non-comparative study was conducted in 215 cancer patients with anemia secondary to chemotherapy with platinum- or non-platinum-based combinations. Epoetin α was administered s.c. (150 IU/kg three times/week) for a planned period of 16 weeks. The response rate of epoetin α, defined as an increase in hemoglobin level of 2 g/dl or more from baseline, was 67%. The rate of response was not related to the chemotherapy regimen administered (platinum or non-platinum based). The percentage of patients transfused and the transfusion rate during epoetin α treatment were reduced. Transfusional need was eliminated in 64 (75%) of the 85 patients transfused before the study start, after 1 month of therapy. Quality of life, assessed using a visual analog scale, improved markedly in patients who experienced a hematological response. These patients also experienced a statistically significant ($p<0.0001$) improvement in mean WHO performance score. These findings indicate that epoetin α is a well tolerated and effective agent which increases hemaglobin concentration and reduces transfusion requirements in anemic cancer patients receiving chemotherapy.

Key words: Anemia, cancer, chemotherapy, epoetin α, platinum.

Introduction

Anemia is a frequent complication of advanced cancer. It may be due to a variety of factors including a deficiency in essential vitamins or minerals, mucosal blood loss or the cytotoxic effects of anti-cancer agents. Many patients require blood transfusions, although these in turn can be associated with a number of problems such as viral infections from contaminated blood, serious allergic reactions or immunosuppression.[1]

Although the exact mechanisms of cancer-related anemia are currently unclear, anemic cancer patients (and patients with anemia due to other chronic diseases) are known to have considerably lower endogenous erythropoietin levels compared to those with anemia due to iron deficiency or blood loss.[2] This does not appear to be dependent on the types of malignancy, but may be related to activation of inflammatory-derived cytokines which, in turn, inhibit erythropoietin production and hematological response.[3-5]

Cytotoxic chemotherapy frequently aggravates the blunted erythropoietin response observed in anemic cancer patients.[6] In some instances, chemotherapeutic agents have direct adverse effects on the bone

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marrow and hematopoietic cells, whereas cisplatin has nephrotoxic effects which are thought to cause damage to erythropoietin-producing cells.[7] However, the finding that erythropoietin levels may also be reduced to a similar extent by non-cisplatin-containing regimens[2] suggests that other mechanisms are also involved.

Promising results have been observed with epoetin α (recombinant human erythropoietin) in anemic patients with hematologic or solid malignancies treated with a wide range of chemotherapeutic regimens. In these preliminary studies epoetin α was well tolerated, and resulted in increased hemoglobin concentrations and hematocrit, and consequently a reduction in transfusion requirements.[8-12]

The goal of the present study was to evaluate the efficacy and safety of epoetin α administered s.c. to cancer patients with anemia receiving cyclic chemotherapy with platinum- or non-platinum-based regimens. The course of anemia and transfusion requirements were assessed, and hematological responses was investigated in relation to initial prognostic factors such as tumor type and/or pre-study transfusion practice. In addition, the effect of correction or reduction of the symptoms of anemia on WHO performance scores and quality of life was examined.

Patients and methods

Eligibility criteria

Male and female patients with anemia secondary to malignancy treated with cyclic chemotherapy (platinum- or non-platinum-based regimens) were eligible for inclusion into this multicenter, open-label, non-comparative study. Anemia was defined as an initial hemoglobin level of 10.5 g/dl or less. In addition, patients were to be at least 18 years old, have been clinically stable for at least 1 month prior to study entry, have a life expectancy of at least 4 months and a WHO performance score of 3 or less.[13] Laboratory eligibility criteria included: neutrophil count >500 cells/mm^3, platelet count $>75\,000$ cells/mm^3, creatinine <2.0 mg/dl, stool negative for occult blood or only one positive and a negative direct Coombs test or a positive test with no evidence of significant active hemolysis.

The study was carried out according to the Declaration of Helsinki and approval was obtained from the appropriate local Ethical Review Committees. All patients provided informed consent.

Treatment schedule

Epoetin α (EPREX®; Cilag AG International, Zurich, Switzerland) was administered s.c. at a dose of 150 IU/kg three times/week for a total of 16 weeks. In an attempt to avoid omission of epoetin α injections, administration on the same day as cyclic chemotherapy was permitted. If the hemaglobin reached a concentration of 12–14 g/dl, one or two doses were withheld as necessary to maintain hemoglobin within this range. Dosage increases were not permitted. Patients who chose to self-administer epoetin α were required to demonstrate their competence to a health-training professional.

Transfusions were administered as necessary based on clinical judgment and practice. Hemoglobin level was determined at the time of transfusion. Iron supplements could be given on the decision of the investigator to ensure that sufficient iron stores, based on laboratory parameters, were available. Iron supplementation was also recommended for all patients, unless laboratory evidence indicated iron overload consequent to repeated transfusions. Concomitant use of androgens was not permitted.

Efficacy and safety analyses

Baseline assessments included a medical history (malignancy history, transfusion requirements for the past 6 months, current therapy, etc.) and physical examination, determination of vital signs and WHO performance score, completion of a quality of life assessment (using a visual analog scale for energy level, ability to do daily activities and overall quality of life), and laboratory analyses including hematology, serum chemistry (including serum iron, ferritin and total iron binding capacity), prothrombin time, urinalysis, stool occult blood and a direct Coombs test. Details regarding epoetin α dose, transfusion requirements, concurrent therapy (including chemotherapy) and any adverse events were documented weekly throughout the study. Recording of vital signs and hematology tests were performed every week during the first 4 weeks of the study and every 2 weeks thereafter. Final evaluations after completion of the study included a physical examination, serum chemistry, urinalysis, determination of WHO performance score, the physician's global evaluation and a quality of life assessment.

The efficacy of epoetin α treatment was assessed based on changes in hemoglobin concentration from baseline and on transfusion data including hemoglobin at the time of transfusion and the number of patients

requiring transfusion before and after therapy. Response to epoetin α therapy was defined as a hemoglobin level increase of 2 g/dl or more from baseline at any time during the final 12 weeks of the study (weeks 5-16), provided no blood transfusion had been adminstered in the 2 weeks preceding the increase. The hemoglobin values of transfused responders were ignored for the day of transfusion and 14 days thereafter. Additional evaluations included the assessment of quality of life, WHO performance scores and the physician's global assessment. Safety assessments included vital signs, laboratory determinations, physical examinations, and the incidence and severity of adverse events.

Statistical methods

Two statistical analyses were performed. The first was a standard intent-to-treat analysis where all patients originally recruited were analyzed for efficiacy and safety. In addition, a per-protocol analysis was undertaken in patients excluding those classified as non-evaluable.

The data from the study were analyzed for both the overall study population and according to the type of chemotherapy regimen: platinum- versus non-platinum-containing chemotherapy regimens. However, an unbiased statistical comparison of the two treatment groups, platinum- versus non-platinum-containing chemotherapy, is not possible because the patients in this study had different tumor types, received different chemotherapy regimens, etc.

Hematological response rate and transfusion requirements were also analyzed by tumor type, demographic factors and anti-cancer treatment. To determine the relationship of response rate to possible prognostic factors such as tumor type and pre-study transfusion requirements, a logistic regression analysis was performed.

Quality of life data and WHO performance scores were statistically summarized. Baseline and termination performance scores were compared by means of a paired *t*-test.

Results

Patient characteristics

A total of 215 anemic cancer patients receiving chemotherapy (116 treated with platinum-based regimens and 99 treated with non-platinum-based regimens) were enrolled in 30 trial centers in 11 different countries (five in Hungary, three each in the CSFR, the Gulf, Pakistan, Poland, Saudi Arabia and Yugloslavia, two each in Greece, Israel and Turkey, and one in Bulgaria). The demographic and baseline characteristics of the 215 patients are shown in Table 1. All patients were analyzed for toxicity. An additional efficacy analysis was performed on 198 patients, which excluded 17 patients with treatment duration of less than 29 days (n=9), baseline hemoglobin above 11.0 g/dl (above 10.5 g/dl by a margin of 0.5 g/dl) (n=6), renal involvement and failure (n=1), and thalassemia (n=1), as mentioned previously. The findings of both efficacy analyses were similar. Thus, for the purposes of the study reported herein, only the findings based on the intent-to-treat analysis are presented.

Patients treated with platinum-based chemotherapy received cisplatin (68%) or carboplatin (24%) or both (8%). For patients treated with non-platinum-based chemotherapy, the most commonly employed compounds were cyclophosphamide (27%), vincristine (25%), bleomycin (21%), 5-fluorouracil (20%) and methotrexate (19%). Cyclophosphamide was also given to 20% of patients receiving platnium-containing combinations.

At the end of the study, the mean weekly dose of epoetin α in the platinum-based chemotherapy group was 151.4 ± 23.3 IU/kg, slightly higher than the mean weekly dose in the non-platinum-based group (138.6 ± 38.6 IU/kg). Seventy-four patients discontinued treatment before the end of the study (Table 2).

A total of 59 patients, known to be iron-deficient before the start of epoetin α therapy (16% of these patients evaluated for serium iron had a baseline level below 8 μmol/l and 13% evaluated for transferrin saturation had a baseline level below 15%), received iron supplements. Thirty-five of these patients were treated with platinum-based chemotherapy and 24 with non-platinum-based chemotherapy. The majority of iron supplements were given orally (28 patients treated with platinum and 22 with non-platinum-based chemotherapy); one patient was treated intravenously and six intramuscularly. Route of administration was unknown in two patients.

Hematological response

Mean hemoglobin concentrations increased steadily throughout the study, with no marked differences between patients treated with platinum- or non-platinum-based chemotherapy (Figure 1). Overall, there was an increase from 9.1 ± 1.3 at baseline to 12.3 ± 2.3 g/dl at the end of the study. A total of 143 epoetin α-treated patients (66.5%) had an increase of at

least 2 g/dl in hemoglobin level from baseline, 81 of whom were treated with platinum-based chemotherapy and 62 with non-platinum-based chemotherapy. The hematological response rates to epoetin α treatment in the groups treated with platinum- and non-platinum-based chemotherapy were 69.8 and 62.6%, respectively. Among the responders, mean hemoglobin level increased from 9.0±1.2 at baseline to 13.0±2.0 g/dl at termination; the corresponding values in the 72 non-responders were from 9.3±1.5 to 10.1±1.6 g/dl, respectively.

Logistic regression analysis failed to demonstrate any significant correlation between hemoglobin response and the following parameters: tumor type, chemotherapy with or without cisplatin, steroid treatment, iron supplementation or transfusion

Table 1. Characteristics of all patients

	Platinum-based chemotherapy (*n*=116)	Non-platinum-based chemotherapy (*n*=99)	Total (*n*=215)
Male/female (*n*)	27/89	34/64[a]	61/153[a]
Mean age±SD (years; range)	50.9±13.5 (13–80)	47.5±13.7 (18–75)	49.3±13.7 (13–80)
Mean weight (kg)±SD (kg; range)	62.3±12.7 (25–102)	65.2±14.0 (36–101)	63.7±13.4 (25–102)
Primary tumor			
gynecological (ovarian, uterus)	62 (53%)	8 (8%)	70 (33%)
breast	10 (9%)	31 (31%)	41 (19%)
lymphoma	2 (2%)	29 (29%)	31 (14%)
lung	10 (9%)	10 (10%)	20 (9%)
gastrointestinal	11 (10%)	5 (5%)	16 (7%)
urogenital (testis, prostate, bladder)	10 (9%)	6 (6%)	16 (7%)
head and neck	5 (4%)	2 (2%)	7 (3%)
other/unknown	6 (5%)	8 (8%)	14 (7%)
Transfusion dependent (*n*)	39 (33.6%)	46 (46.5%)	85 (39.5%)
Mean units transfused within the last 6 months ±SD (range)	3.33±2.8 (1–16) (*n*=39)	5.76±5.2 (1–23) (*n*=45)	4.63±4.4 (1–23) (*n*=84)
Mean hemoglobin level (g/dl)±SD (g/dl; range)	9.3±1.3 (6–14) (*n*=116)	8.83±1.2 (5–11) (*n*=97)	9.10±1.3 (5–14) (*n*=215)
Mean hematocrit level±SD (%; range)	28.16±4.1 (19–41) (*n*=115)	26.71±4.2 (13–36) (*n*=97)	27.49±4.2 (13–41) (*n*=212)
Neutrophils (*n*)			
$<1\times10^9$/l	9 (8.0%)	11 (12.8%)	20 (10.1%)
$\geqslant1\times10^9$/l	103 (92.0%)	75 (87.2%)	178 (89.9%)

[a]Data missing for one patient.

Table 2. Reasons for premature discontinuation

	Platinum-based chemotherapy (*n*)	Non-platinum based chemotherapy (*n*)	Total (*n*)
Disease progression and /or toxicity of chemotherapy	11	21	32
Personal reasons/lack of compliance/loss to follow-up	9	8	17
Sufficient hemoglobin level	6	7	13
Adverse events	1	2	3
Other[a]	6	3	9
Total	33 (28.4%)	41 (41.4%)	74 (34.4%)

[a]Other reasons: missing data records (*n*=4), death (*n*=3), septic shock (*n*=1), ineligible due to thalassemia (*n*=1).

dependence. However, correlation between hemoglobin response and baseline hemoglobin level was found to approach statistical significance (p=0.015). Moreover, the highest rates of response were observed in patients with gastrointestinal (75%) and breast cancers (71%), lymphoma (68%), and ovarian cancer (67%).

Increases were also seen in mean weekly hematocrit values, which ranged from baseline 28.2±4.1 to 37.7±6.6% at termination in patients treated with platinum-based chemotherapy and from 26.7±4.2 to 37.1±8.0% in those treated with non-platinum-based chemotherapy. There were no marked differences between the groups treated with platinum- and non-platinum-based chemotherapy with respect to absolute neutrophil count over time.

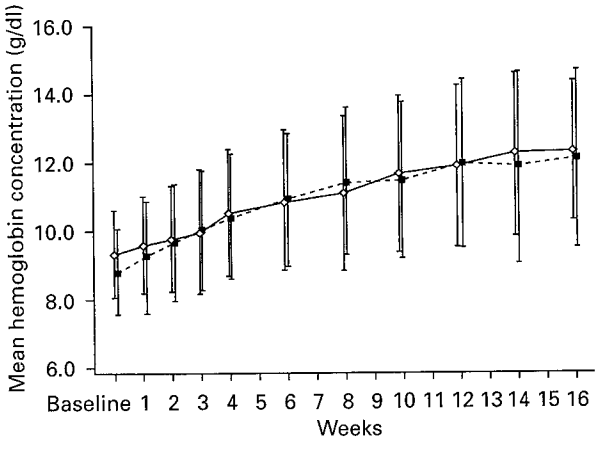

Figure 1. Mean weekly concentrations of hemoglobin (g/dl) throughout the study in patients treated with platinum-based (n=116, ◇) or non-platinum-based (n=99, ■) chemotherapy.

Transfusion requirements

The percentage of patients transfused and the mean rate of transfusion by chemotherapy and pre-treatment transfusion status are shown in Table 3. The proportion of patients requiring transfusion in the pre-study period (6 months) was lower in the platinum-based chemotherapy group than in the non-platinum-based chemotherapy group (33.6 versus 46.5%, respectively). During weeks 5-16 of the study, the cumulative numbers of transfused patients were similar in the two chemotherapy groups (23 versus 21%, respectively). The percentage of patients requiring transfusion during this study period was higher in non-responders to epoetin α (20/62; 32%) than in responders (25/143; 18%). The overall amount of blood used throughout the study fell from 0.62 U/patient during the first month of epoetin α therapy to 0.30U /patient during the final month, with no differences observed between the two chemotherapy regimens.

The need for transfusion was eliminated in 64 (75%) of the 85 patients transfused before the start of the

Table 3. Percentage of patients transfused and mean transfusion rate (units/patient/period) according to chemotherapy and pre-treatment transfusion status

Period[a]	Chemotherapy		Pre-treatment transfusion status		
	Platinum-based (n=116)	Non-platinum-based (n=99)	Transfused (n=85)	Not transfused (n=130)	Overall (n=215)
Number (%) of patients transfused					
pre-study	**39/116 (33.6)**	**46/99 (46.5)**	**85/85 (100)**	**0/130 (0.0)**	**85/215 (39.5)**
week1–4	23/116 (19.8)	23/99 (23.2)	25/85 (29.4)	21/130 (16.2)	46/215 (21.4)
week 5–8	17/115 (14.8)	12/90 (13.3)	13/81 (16.0)	16/124 (12.9)	29/205 (14.1)
week 9–12	12/111 (10.8)	9/80 (11.3)	12/76 (15.8)	9/115 (7.8)	21/191 (11.0)
week 13–16	10/96 (10.4)	6/71 (8.5)	9/65 (13.8)	7/102 (6.9)	16/167 (9.6)
week 5–16	**26/115 (22.6)**	**19/90 (21.1)**	**21/81 (25.9)**	**24/124 (19.4)**	**45/205 (22.0)**
Mean (±SD) transfusion rate (U/patient)					
pre-study	**1.20±0.22**	**2.84±0.51**	**4.96±0.54**	**0.00±0.00**	**1.96±0.27**
week1–4	0.59±0.15	0.67±0.14	0.86±0.20	0.47±0.11	0.62±0.10
week 5–8	0.38±0.10	0.36±0.12	0.50±0.14	0.29±0.08	0.37±0.07
week 9–12	0.27±0.09	0.29±0.10	0.45±0.14	0.17±0.05	0.28±0.07
week 13–16	0.31±0.11	0.28±0.13	0.54±0.19	0.15±0.06	0.30±0.08
week 5–16	**0.91±0.20**	**0.84±0.23**	**1.35±0.33**	**0.56±0.12**	**0.88±0.15**

[a]Note that the different periods are not comparable due to individual drop-outs and various observation times (pre-study period was 6 months; week 5–16, 3 months; other periods, 1 month).

study and, of the 130 patients who were not initially transfused, only 24 (19%) required transfusion after 1 month of therapy. The mean number of units transfused in the 66 patients who were transfused during both the pre-study and study periods fell from 2.04 in the first month of the study to 1.00 U/patient in the final month, mainly due to marked reductions in transfusion requirement in epoetin α-treatment responders.

The overall mean hemoglobin value at transfusion (i.e. the trigger for transfusion) was virtually unchanged during the study (7.59 g/dl) compared to baseline (7.87 g/dl), thus suggesting that there were no significant modifications in transfusion practices.

Quality of life, performance scores and global assessment

All three parameters included in the quality of life evaluation (energy level, daily activity and overall quality of life) were improved by a similar extent at the end of the study (Table 4). The improvements seen in patients treated with non-platinum-based chemotherapy were somewhat greater than those in patients treated with platinum-based chemotherapy, although both groups had comparable baseline values. Improvements were more frequently seen in patients who achieved an increase in hemoglobin level of at least 2 g/dl from baseline than in those who did not.

An overall improvement was also observed in mean WHO performance scores (mean change from baseline to termination; -0.4 ± 1.2), with the percentage of patients acheiving a score of 0 increasing from 11% at baseline to 27% at the end of the study. This was accompanied by a reduction in the percentage of patients scoring 2 or more from 47% at baseline to 23% at the end of the study. Similar improvements were noted in patients treated with platinum-based and non-platinum-based chemotherapy. Patients with hemoglobin level increases of at least 2 g/dl from baseline achieved considerably better scores than those who did not respond to epoetin α therapy (Figure 2). The mean improvement observed in patients with hematological rseponse (-0.6 ± 0.1) was highly statistically significant (p=0.0001). No significant change (0.1 ± 0.2; p=0.74, paired t-test) was observed in patients without a hematological response.

The physicians' global assessment of treatment efficacy was performed in 171 patients; study treatment was classified as 'good'/'very good'/'excellent' in 143 of these patients (84%) and 'poor'/'fair' in the remaining 28 (16%). There were no marked differences between the findings in the platinum and non-platinum chemotherapy-based groups.

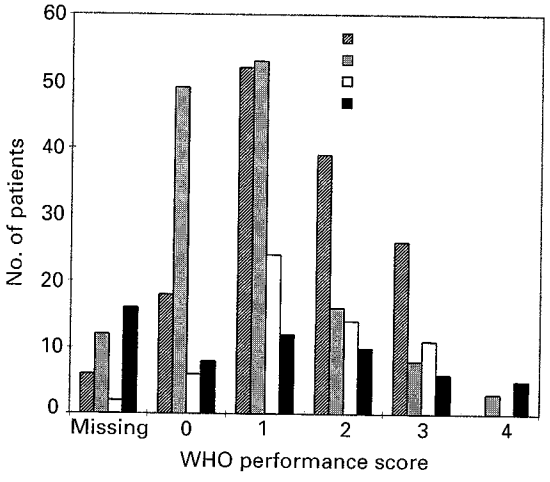

Figure 2. WHO performance scores before and after treatment in responders (patients experiencing an increase from baseline level of hemoglobin of at least 2 g/dl during the study) and non-responders. *Those patients for whom data were not available were defined as missing.

Table 4. Mean ± SD (n) quality of life measures (0–10 cm) at baseline and at endpoint, according to chemotherapy and hematological responses

	Chemotherapy			Hematological response		
	Platinum-based (n=116)	Non-platinum-based (n=99)	Overall (n=215)	Responders (n=143)	Non-responders (n=72)	Overall (n=215)
Energy level (n) baseline	4.9±2.37 (113)	4.4±2.18 (95)	4.6±2.29 (208)	4.6±2.22 (140)	4.8±2.45 (68)	4.6±2.29 (208)
change[a]	1.5±3.01 (99)	2.2±2.66 (66)	1.8±2.88 (165)	2.3±2.56 (123)	0.4±3.34 (42)	1.8±2.88 (165)
Daily activity (n) baseline	4.7±2.52 (113)	4.7±2.31 (94)	4.7±2.42 (207)	4.6±2.35 (140)	4.9±2.57 (67)	4.7±2.42 (207)
change[a]	1.7±3.30 (99)	2.1±2.82 (65)	1.9±3.11 (164)	2.4±2.79 (123)	0.3±3.51 (41)	1.9±3.11 (164)
Quality of life (n) baseline	5.0±2.58 (112)	5.0±2.26 (93)	5.0±2.43 (205)	4.8±2.37 (138)	5.2±2.56 (67)	5.0±2.43 (205)
change[a]	1.9±2.97 (98)	2.0±2.62 (66)	1.9±2.83 (164)	2.3±2.73 (122)	0.8±2.84 (42)	1.9±2.83 (164)

[a]Positive change reflects improvement.

Safety and tolerability

Treatment with epoetin α was well tolerated. In total, there were 83 reported adverse events in the patients undergoing cyclic chemotherapy. The events most commonly reported in both chemotherapy groups were associated with the cardiovascular and gastrointestinal systems and the body as a whole. Of these, 13 were considered to have a possible or definite relationship to epoetin α therapy. Three patients experienced blood pressure anomolies and one experienced mild tachycardia. One patient, who experienced a rise in blood pressure after week 13, discontinued epoetin α therapy. Of note, six patients receiving platinum-containing chemotherapy experienced skin and s.c. tissue adverse events, whereas this was observed in only one patient in the non-platinum-containing chemotherapy group. Three patients experienced transient skin reaction at the injection site as a result of epoetin α administration. This did not require discontinuation of therapy. There were 31 deaths during the study, none of which were related to epoetin α therapy.

Discussion

Anemia is a frequent condition in cancer patients which tends to worsen with the progression of the disease and with the administration of chemotherapy. Cisplatin treatment is known to be nephrotoxic and it has been suggested that this may result in damage to erythropoietin-producing cells leading to anemia.[7-14] However, a normal endogenous erythropoietin response to declining hemoglobin levels has been observed in patients treated with consecutive cycles of cisplatin.[15] Cisplatin-treated patients have also been shown to develop severe anemia without underlying renal failure.[7] Moreover, a normal erythropoietin response to anemia has been reported in patients treated with cisplatin or non-cisplatin chemotherapy.[2] The results from the current study indicated that concomitant chemotherapy with platinum-containing regimens clearly did not compromise the efficacy of epoetin α in stimulating erythropoiesis, with similar overall response rates observed in the groups treated with platinum-based and non-platinum-based chemotherapy (70 and 63%, respectively). This suggests that mechanisms other than nephrotoxicity are also involved in the development of anemia secondary to chemotherapy.

The overall response rate to epoetin α therapy of 67% was impressive, but might have been improved further if dose escalation had been permitted in patients who did not experience a hematological response. This presumption is supported by data from open-label studies following on from a large multicenter double-blind placebo-controlled study.[8,16,17] During the double-blind part of the study, patients not receiving chemotherapy were administered 300 IU/kg/week epoetin α for 8 weeks, whereas patients receiving chemotherapy (divided into two groups: receiving cisplatin or not receiving cisplatin) were administered epoetin α 450 IU/kg/week for 12 weeks. Following completion of the double-blind phase, patients received epoetin α on an open-label basis, with a dose titration of up to 900 IU/kg/week to achieve and maintain a hematocrit of 38%. During the first month of therapy, the percentage of patients transfused was 58% in the group not receiving chemotherapy, and 64 and 70%, respectively, in those groups receiving chemotherapy with or without cisplatin. During month 6 of therapy, however, these percentages fell to 10% in the group not receiving chemotherapy, and to 12 and 13% in the groups receiving chemotherapy with or without cisplatin, indicating that epoetin α administration can result in prolonged decreased transfusion requirements.

In the present study both groups showed comparable myelosuppression, as reflected by similar neutrophil counts over time. This provides further evidence that the effect of epoetin α in overcoming inhibition of erythroid proliferation is not adversely affected by platinum-containing regimens.

Apart from baseline hemaglobin values, none of the initial parameters investigated (platinum treatment, steroid treatment, iron supplementation and transfusion dependency) were shown to have a statistically significant relationship to hematological response to epoetin α therapy. Also demographic factors were not predictive for hematological response.

As a result of increases in hemoglobin concentration, the monthly percentage of patients requiring transfusion and the rate of transfusion steadily decreased throughout the study period. Again, there were no marked differences between the groups treated with platinum- or non-platinum-containing regimens.

Benefits were also observed in the individual transfusion requirements of the patients, with the need for transfusion after 1 month being eliminated in 75% of patients who were transfused before the start of the study. Moreover, only 19% of patients who were not initially transfused required transfusion after 1 month. It is also interesting to note that the mean hemoglobin concentration at the end of the study was approximately 1.4 g/dl lower in the patients who received transfusions during the study compared with

those who were not transfused. This further suggests that epoetin α has benefits over blood transfusion in treating anemia.

The increases in hemoglobin levels and reductions in transfusion requirements seen in patients who experienced an increase of at least 2 g/dl in hemoglobin level from baseline during treatment with epoetin α were translated into overall improvements in quality of life and performance score. Quality of life, assessed using a visual analog scale to monitor energy level, ability to do daily activities and overall quality of life improved markedly in patients who experienced a hematological response. These patients also experienced a statistically significant ($p > 0.0001$) improvement in mean WHO performance score. The post-study shift-down of a small number of responders and non-responders to a WHO performance score of 4 was thought to be attributable to disease progression during the study period.

Comparative cost analyses for epoetin α versus transfusion in cancer patients were not available for each of the participating centers in this study. However, evidence exists in previous studies, of conditions other than cancer, that epoetin α provides hematological recovery benefits at a level of cost-effectiveness over transfusion.[18] In seriously incapitated transfusion-dependent patients, epoetin can also produce a competitive cost per quality-adjusted life-year.[19]

As reported in previous studies,[10,20] treatment with epoetin α was well tolerated. The only adverse event which was considered 'definitely' related to study treatment was pain at the injection site and this was observed in only three patients. An increase in blood pressure was also noted in three patients but resulted in treatment withdrawal in only one. These effects may have been caused by an inappropriate increase in red blood cell mass[8] and may have been prevented by monitoring the initial blood pressure.

In conclusion, this study has shown that epoetin α (150 IU/kg) three times/week is a well tolerated and effective treatment resulting in increased hemoglobin concentrations and decreased transfusion requirements in anemic cancer patients treated with chemotherapy. These objective benefits also appear to be associated with marked improvements in the performance scores and general quality of life of patients with response to epoetin α therapy.

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References

1. Blumberg N, Heal JM. Effects of transfusion on immune function. Cancer recurrence and infection. *Arch Pathol Lab Med* 1994; **118:** 371-9.
2. Miller CB, Jones RJ, Piantadosi S, *et al.* Decreased erythropoietin response in patients with anemia of cancer. *New Engl J Med* 1990; **322:** 1689-92.
3. Doweiko JP, Goldberg MA. Erythropoietin therapy in cancer patients. *Oncology* 1991; **5:** 31-7.
4. Jelkmann W, Wolf M, Fandrey J. Inhibition of erythropoietin production by cytokines and chemotherapy may contribute to the anemia in malignant diseases. In: Vaupel P, ed. *Oxygen transport to tissue XV.* New York: Plenum Press 1994: 525-30.
5. Schooley JC, Kullgren B, Allison AC. Inhibition by interleukin-1 of the action of erythropoietin on erythroid precursors and its possible role in the pathogenesis of hypoplastic anaemias. *Br J Haematol* 1987; **67:** 11-7.
6. Schapira L, Antin JH, Ransil BJ, *et al.* Serum erythropoietin levels in patients receiving intensive chemotherapy and radiotherapy. *Blood* 1990; **76:** 2354-9.
7. Rothmann SA, Paul P, Weick JK, *et al.* Effect of *cis*-diamminedichloroplatinum on erythropoietin production and hematopoietic progenitor cells. *Int J Cell Cloning* 1985; **3:** 415-23.
8. Abels RI, Larholt KM, Krantz KD, *et al.* Recombinant human erythropoietin (epoetin alfa) for the treatment of the anemia of cancer. In: Murphy MJ, ed. *Blood cell growth factors: their present and future use in hematology and oncology (Proc Beijing Symp).* Dayton, OH: Alpha Medical Press 1991: 121-41.
9. Platanias LC, Miller CB, Mick R, *et al.* Treatment of chemotherapy-induced anaemia with recombinant human erythropoietin in cancer patients. *J Clin Oncol* 1991; **9:** 2021-6.
10. Abels R. Erythropoietin for anaemia in cancer patients. *Eur J Cancer* 1993; **29A** (suppl 2): S2-8.
11. Ludwig H, Fritz E, Leitgeb C, *et al.* Erythropoietin treatment for chronic anemia of selected hematological malignancies and solid tumors. *Ann Oncol* 1993; **4:** 161-7.
12. Case DC, Bukowski RM, Carey RW, *et al.* Recombinant human erythropoietin therapy for anemic cancer patients on combination chemotherapy. *J Natl Cancer Inst* 1993; **85:** 801-6.
13. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer* 1981; **47:** 207-14.
14. Smith DH, Goldwasser E, Vokes EE. Serum immunoerythropoietin levels in patients with cancer receiving cisplatin-based chemotherapy. *Cancer* 1991; **68:** 1101-5.
15. Onat H, Inanc SE, Dalay N, *et al.* Effect of cisplatin on erythropoietin and iron changes. *Eur J Cancer Part A Gen Top* 1993; **29A:** 777.
16. Henry DH, Abels RI. Recombinant human erythropoietin in the treatment of cancer and chemotherapy-induced anemia: results of double-blind and open-label follow-up studies. *Semin Oncol* 1994; **21** (suppl 3): 21-8.

17. Nelson RA, Guilfoyle MC, Abels RI, *et al.* Long-term treatment of anemic cancer patients with recombinant human erythropoietin. *Blood* 1992; **80** (suppl 1): 284A (abstr 1126).
18. Sheingold S, Churchill D, Muirhead N, *et al.* The impact of recombinant human erythropoietin on medical care costs for hemodialysis patients in Canada. *Soc Sci Med* 1992; **34:** 983–91.
19. Leese B, Hutton J, Maynard A. A comparison of the costs and benefits of recombinant human erythropoietin (epoetin) in the treatment of chronic renal failure in 5 European countries. *PharmacoEconomics* 1992; **1:** 346–56.
20. Ludwig H, Fritz E, Kotzmann H, *et al.* Erythropoietin treatment of anemia with multiple myeloma. *New Engl J Med* 1990; **332:** 1693–9.

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