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Efficacy and safety of darbepoetin alfa in anaemic patients with lymphoproliferative malignancies: a randomized, double-blind, placebo-controlled study

Michael Hedenus,[1] Magnus Adriansson,[2] Jesus San Miguel,[3] Mark H. H. Kramer,[4] Martin R. Schipperus,[5] Eeva Juvonen,[6] Kerry Taylor,[7] Andrew Belch,[8] Albert Altés,[9] Giovanni Martinelli,[10] David Watson,[11] James Matcham,[11] Gregory Rossi[12] and Timothy J. Littlewood[13] on Behalf of the Darbepoetin Alfa 20000161 Study Group [1]*Department of Internal Medicine, Sundsvall Hospital, Sundsvall, Sweden,* [2]*Department of Internal Medicine, Kalmar Hospital, Kalmar, Sweden,* [3]*Department of Haematology, Hospital Universitario de Salamanca, Salamanca, Spain,* [4]*Department of Haematology, Meander Medisch Centrum, Amersfoort, the Netherlands,* [5]*Department of Haematology, Ziekenhuis Leyenburg, The Hague, the Netherlands,* [6]*Department of Medicine, Helsinki University Central Hospital, Helsinki, Finland,* [7]*Haematology Department, Mater Misericordiae Hospital, South Brisbane, Qld, Australia,* [8]*Department of Medicine, Cross Cancer Institute, Edmonton, Canada,* [9]*Department of Haematology, Hospital Santa Creu I Sant Pau, Barcelona, Spain,* [10]*Haematology Unit, European Institute of Oncology, Milano, Italy,* [11]*Amgen Ltd, Cambridge, UK,* [12]*Amgen Inc., Thousand Oaks, CA, USA, and* [13]*Department of Haematology, Oxford Radcliffe Hospital, Oxford, UK*

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Summary. This phase 3, randomized, double-blind, placebo-controlled study was designed to evaluate the efficacy and safety of darbepoetin alfa in anaemic patients with lymphoproliferative malignancies. Patients ($n = 344$) with lymphoma or myeloma received darbepoetin alfa 2·25 μg/kg or placebo s.c., once weekly for 12 weeks. The percentage of patients achieving a haemoglobin response was significantly higher in the darbepoetin alfa group (60%) than in the placebo group (18%) ($P < 0·001$), regardless of baseline endogenous erythropoietin level. However, increased responsiveness was observed in patients with lower baseline erythropoietin levels. Darbepoetin alfa also resulted in higher mean changes in haemoglobin than placebo from baseline to the last value during the treatment phase (1·80 g/dl *vs* 0·19 g/dl) and after 12 weeks of treatment (2·66 g/dl *vs* 0·69 g/dl). A significantly lower percentage of patients in the darbepoetin alfa group received red blood cell transfusions than in the placebo group ($P < 0·001$). The efficacy of darbepoetin alfa was consistent for patients with lymphoma or myeloma. Improvements in quality of life were also observed with darbepoetin alfa. The overall safety profile of darbepoetin alfa was consistent with that expected for this patient population. Darbepoetin alfa significantly increased haemoglobin and reduced red blood cell transfusions in patients with lymphoproliferative malignancies receiving chemotherapy.

Keywords: anaemia, cancer, erythropoietin, myeloma, lymphoma.

Anaemia is a frequent and often under-appreciated complication of cancer and its treatment that has a multifactorial aetiology, including direct effects of the malignancy itself and the myelosuppressive effects of chemotherapy (Casadevall, 1998; Ludwig & Fritz, 1998; Groopman & Itri, 1999). Anaemia appears to be particularly prevalent in patients with lymphoproliferative malignancies, leading to symptoms of fatigue, dizziness, dyspnoea and functional impairment with associated poor disease outcomes, morbidity and reduced quality of life (Cabanillas *et al*, 1978; Straus *et al*, 1990; Leonard *et al*, 1991; Coiffier, 2000).

Patients with severe or symptomatic anaemia are often treated with red blood cell (RBC) transfusions. However, RBC transfusions may themselves carry the potential risk of serious haemolytic reactions, immunosuppression or

Correspondence: Michael Hedenus, MD, Department of Internal Medicine, Sundsvall Hospital, Sundsvall S-851 86, Sweden. E-mail: Michael.Hedenus@lvn.se

infection (Walker, 1987). Erythropoietic agents such as epoetin or darbepoetin alfa have provided another treatment option for anaemic patients with cancer and have been shown to reduce the need for transfusions in this setting (Abels, 1992; Vansteenkiste *et al,* 2002). Previous studies have indicated that epoetin increases haemoglobin concentrations, relieves the symptoms of anaemia, improves health-related quality of life (HRQOL) and reduces transfusion requirements in patients with solid tumours (Nowrousian, 1998) or lymphoproliferative malignancies (Cazzola *et al*, 1995; Österborg *et al*, 1996, 2002). Similar results regarding the efficacy or safety of epoetin between tumour types have been reported in studies that evaluated patients with a variety of solid or haematological tumours (Demetri *et al*, 1998; Gabrilove *et al,* 2001; Littlewood *et al,* 2001; Bohlius *et al,* 2002; Hedenus *et al,* 2002; Österborg *et al,* 2002). Although epoetin has been evaluated in a broad range of solid tumour types, studies in the lymphoproliferative setting have mainly included patients with multiple myeloma (Ludwig *et al*, 1990; Barlogie & Beck, 1993; Garton *et al*, 1995; Silvestris *et al*, 1995; Mittelman *et al*, 1997; Dammacco *et al,* 2001). In these studies, epoetin was generally administered three times weekly.

Darbepoetin alfa is a unique erythropoietic protein with greater sialic acid content, a longer terminal half-life and greater biological activity than epoetin (Egrie *et al*, 1993), allowing less-frequent administration with a similar efficacy and safety profile (Macdougall *et al*, 1999; Kotasek *et al,* 2000; Glaspy *et al,* 2002). Previous studies of darbepoetin alfa have demonstrated that it is effective for the treatment of anaemia across a wide range of tumour types, with a similar dose–response curve observed in solid tumours and lymphoproliferative malignancies (Hedenus *et al,* 2001). Furthermore, a phase 3, randomized, double-blind, placebo-controlled study conducted in patients with lung cancer confirmed that a darbepoetin alfa starting dose of 2·25 μg/kg administered once weekly significantly reduced the percentage of patients who required a RBC transfusion and increased haemoglobin concentrations compared with placebo (Vansteenkiste *et al,* 2002).

Results from a phase 2 study in patients with lymphoma or myeloma demonstrated that darbepoetin alfa also significantly increased haemoglobin concentrations relative to placebo at doses of 1·0–4·5 μg/kg/week (Hedenus *et al,* 2002). To further evaluate the effects of darbepoetin alfa on haemoglobin concentrations and RBC transfusions in patients with lymphoproliferative malignancies, we conducted a phase 3, randomized, double-blind, placebo-controlled study. The study included patients with myeloma and lymphoma, and was stratified to enable a comparison of darbepoetin alfa and placebo within each malignancy type.

PATIENTS AND METHODS

Patients. Independent ethics committees for each of the 49 recruiting centres in Europe, Australia and Canada approved the study, and all patients provided written informed consent before any study-specific procedures were performed. Broad eligibility criteria were selected to enable the evaluation of darbepoetin alfa in a representative and heterogeneous population of patients with lymphoproliferative malignancies (e.g. no endogenous erythropoietin entry requirement and no lower limit for haemoglobin concentration). Men or women ≥ 18 years of age who had a diagnosis of lymphoproliferative malignancy [Hodgkin's disease, non-Hodgkin's lymphoma (regardless of grade), chronic lymphocytic leukaemia, or multiple myeloma] and at least 12 additional planned weeks of chemotherapy were eligible to participate in the study. Patients were required to have anaemia (haemoglobin concentration ≤ 11·0 g/dl) primarily due to cancer or chemotherapy (i.e. serum folate ≥ 4·5 nmol/l and vitamin B_{12} ≥ 148 pmol/l, no haemolysis, and no gastrointestinal bleeding), a life expectancy of ≥ 4 months, an Eastern Cooperative Oncology Group (ECOG) performance status of 0–3, and adequate renal function (serum creatinine concentration ≤ 177 μmol/l) and liver function (serum bilirubin ≤ 1·5 times the central laboratory upper limit of normal).

Patients were excluded from the study if they had Burkitt's or lymphoblastic lymphoma, were scheduled to receive a stem cell transplant within 16 weeks of randomization, or had received myeloablative chemotherapy, radiotherapy for transplantation, or chemotherapy regimens containing investigational agents. Other exclusion criteria included: transferrin saturation < 15% and ferritin < 10 μg/l; significant central nervous system, cardiac, or inflammatory diseases; or any known primary haematological disorders that could cause anaemia. Patients were not to have received epoetin within 8 weeks, > 2 RBC transfusions within 4 weeks, or any RBC transfusion within 2 weeks before randomization.

Study design. This was a multicentre, randomized, double-blind, placebo-controlled study in patients with lymphoproliferative malignancies who were receiving chemotherapy. Eligible patients were randomized in a 1:1 allocation, by a central randomization service, to receive darbepoetin alfa 2·25 μg/kg or placebo, administered s.c. once weekly for 12 weeks. Randomization was stratified to balance the treatment groups with respect to malignancy type (lymphoma *vs* myeloma), region (Australia *vs* Canada *vs* Western Europe) and chemotherapy before randomization (heavily pretreated *vs* not heavily pretreated). Patients were considered heavily pretreated if they received two or more lines of chemotherapy, or one line of chemotherapy and a stem cell transplant.

The dose of study drug was to be doubled for patients who had an inadequate increase in haemoglobin (≤ 1·0 g/dl from baseline after 4 weeks of treatment). The study drug was to be withheld if a patient's haemoglobin value increased to > 15·0 g/dl for men or > 14·0 g/dl for women, and was to be reinstated at 50% of the previous weekly dose once the haemoglobin concentration decreased to ≤ 13·0 g/dl. Iron therapy and RBC transfusion policies were left to the discretion of the investigators, although transfusions were recommended for patients with haemoglobin concentrations ≤ 8·0 g/dl. Patients completed a 4-week follow-up evaluation after the last dose of study drug, with

further long-term collection of disease status and survival information at regular intervals.

Study drug. Darbepoetin alfa (Aranesp®; Amgen Inc., Thousand Oaks, CA, USA) was supplied in vials as a clear, colourless, sterile protein solution containing 500 μg/ml darbepoetin alfa. Placebo (sterile darbepoetin alfa vehicle) was supplied in identical vials.

Study endpoints. Efficacy was assessed using haemoglobin endpoints and the incidence of RBC transfusions. The primary measure of efficacy was the percentage of patients achieving a haemoglobin response, defined as an increase in haemoglobin of ≥ 2·0 g/dl from baseline in the absence of any RBC transfusions during the previous 28 d. The main secondary efficacy endpoint was the incidence of RBC transfusions from week 5 to the end of the treatment phase, which is consistent with previous studies of epoetin (Abels *et al*, 1991; Dammacco *et al*, 2001; Littlewood *et al*, 2001), although the incidence of RBC transfusions from week 1 to the end of the treatment phase was also analysed. An additional, prospectively defined efficacy endpoint was the change in haemoglobin from baseline. The percentage of patients that achieved a haematopoietic response (haemoglobin response or a haemoglobin concentration ≥ 12·0 g/dl in the absence of any RBC transfusions during the previous 28 d) during the treatment period, which has been frequently reported in published studies of erythropoietic agents (Demetri *et al*, 1998; Gabrilove *et al*, 2001; Vansteenkiste *et al*, 2002), was also calculated to enable comparison with previous results.

The primary HRQOL scale in this study was the Functional Assessment of Cancer Therapy (FACT)-Fatigue subscale, which has been validated in the oncology setting (Cella, 1997). The 13-question subscale has scores that range from 0 to 52, with higher scores indicating less fatigue. Patients completed the HRQOL questionnaire, which included the FACT-Fatigue subscale, every 4 weeks on d 1 of each cycle of chemotherapy, before any other study procedures.

Safety was assessed by summarizing the incidence of adverse events by treatment group, and by evaluating the formation of antibodies resulting from darbepoetin alfa administration. Three validated assays were used to evaluate antibody formation. The first was a radioimmunoprecipitation (RIP) screening assay to detect seroreactivity to darbepoetin alfa. Any RIP-reactive samples were to be further evaluated using a cell-based bioassay to detect neutralizing or inhibiting effects on the activity of darbepoetin alfa, and a BIAcore assay (Biacore International, AB, Uppsala, Sweden) to confirm the presence of antibodies and to characterize the nature of the binding and the antibody classes observed.

Disease status and survival information continue to be collected during a long-term follow-up period.

Statistical analysis. The planned sample size of 340 patients (85 patients per treatment group per malignancy type) was selected, to allow for the detection of an increase in haemoglobin response rates from 25% in the placebo group to 50% in the darbepoetin alfa group within each malignancy type with 90% power at a two-sided significance level of 0·05. This sample size took into consideration an estimated withdrawal rate of 10% during the 12-week study. All patients who received at least one dose of study drug were included in the analyses of efficacy and safety [intent-to-treat (ITT) analysis set], with the exception of transfusion endpoints evaluated during week 5 to the end of the treatment phase. For these endpoints, patients who did not complete the first 4 weeks of treatment were excluded from the analysis.

The Kaplan–Meier method was used to estimate the percentages of patients with a haemoglobin response, haematopoietic response or RBC transfusion, because of the anticipated withdrawal rate. For haemoglobin and haematopoietic response, patients who withdrew from the study early for any reason were censored at the time of withdrawal. For the RBC transfusion endpoints, patients who withdrew from the study before the completion of the treatment period were considered to have been transfused, and patients who withdrew because of either disease progression or death were censored at the time of withdrawal. Approximate 95% confidence intervals (CI) for the Kaplan–Meier estimates were calculated using Greenwood's formula (Kalbfleisch & Prentice, 1980). Crude estimates were also calculated as a sensitivity analysis, but as the results were consistent with the Kaplan–Meier estimates, only the Kaplan–Meier estimates are reported. Statistical comparisons of these percentages between treatment groups were based on the chi-squared test.

Baseline serum erythropoietin has previously been identified as a possible factor influencing the response to erythropoietic agents in patients with lymphoproliferative malignancies (Ludwig *et al*, 1990; Österborg *et al*, 1996). Thus, Cox proportional hazards modelling was performed as an exploratory analysis to evaluate the effect of baseline serum erythropoietin (≤ 100 *vs* > 100 IU/l) on the time to haemoglobin response.

The mean (± standard error of the mean, SEM) change in haemoglobin concentration was assessed in two ways: first, by subtracting the baseline haemoglobin value from the last value during the treatment phase; and, second, by evaluating the subset of patients who completed at least 12 weeks of treatment. Haemoglobin values within 28 d after a RBC transfusion were excluded from this analysis.

Efficacy endpoints were analysed with and without adjusting for the stratification factors of malignancy type, region and chemotherapy before randomization. Results of these analyses were similar; thus, only the results of the unadjusted analyses are presented.

Exploratory analyses of changes in the FACT-Fatigue subscale were conducted using analysis of variance (ANOVA). The relationship between the change in the FACT-Fatigue subscale and the change in haemoglobin was investigated using simple linear regression.

RESULTS

Patient demographics and disposition

A total of 349 patients were randomized into the study, 176 to darbepoetin alfa and 173 to placebo. Five patients withdrew from the study before receiving the first dose of

study drug; thus, 344 patients (99%) were included in the ITT population and the efficacy and safety analyses. Three hundred and thirty-two patients (167 darbepoetin alfa, 165 placebo) completed at least 28 d of treatment and were included in the analysis of RBC transfusions from week 5 to the end of the treatment phase. One patient was randomized to receive placebo, but received darbepoetin alfa as the result of an error at the study centre. Efficacy data for this patient were analysed in the placebo group, and safety data were analysed in the darbepoetin alfa group.

Patient baseline demographic and clinical characteristics were generally well balanced between the treatment groups (Table I). Overall, half of the patients had a diagnosis of lymphoma and half had a diagnosis of myeloma. The proportions of patients with each malignancy type were similar between treatment groups.

A total of 293 patients (84%) completed the study, with a similar number of patients in the darbepoetin alfa and placebo groups (Fig 1). As expected in this population, delay or discontinuation of chemotherapy, death, adverse events and consent withdrawal were the most frequent reasons for withdrawal from the study.

Effects on haemoglobin

Haemoglobin response. Darbepoetin alfa increased the percentage (95% CI) of patients achieving a haemoglobin response from 18% (95% CI 12, 24) in the placebo group to 60% (95% CI 52, 68) in the darbepoetin alfa group (Fig 2), a

Table I. Baseline demographic and clinical characteristics.

	Darbepoetin alfa	Placebo	Total
Number of patients	174	170	344
Sex, *n* (%)			
Men	87 (50%)	78 (46%)	165 (48%)
Women	87 (50%)	92 (54%)	179 (52%)
Age, years			
Mean (SD)	64·8 (13·8)	64·6 (12·2)	64·7 (13·0)
Malignancy type, *n* (%)			
Lymphoma	85 (49%)	86 (51%)	171 (50%)
Hodgkin's disease	12 (7%)	9 (5%)	21 (6%)
NHL*	44 (25%)	51 (30%)	95 (28%)
CLL	29 (17%)	26 (15%)	55 (16%)
Multiple myeloma	89 (51%)	84 (49%)	173 (50%)
ECOG performance status, *n* (%)			
0	54 (31%)	43 (25%)	97 (28%)
1	80 (46%)	92 (54%)	172 (50%)
2	32 (18%)	28 (16%)	60 (17%)
> 2	8 (5%)	6 (4%)	14 (4%)
Unknown	0 (0%)	1 (1%)	1 (< 1%)
Prior chemotherapy, *n* (%)			
Heavily pretreated†	46 (26%)	47 (28%)	93 (27%)
Not heavily pretreated	128 (74%)	123 (72%)	251 (73%)
Haemoglobin, g/dl			
Mean (SD)	9·59 (1·22)	9·50 (1·21)	9·54 (1·21)
Serum endogenous EPO, mU/ml			
n	173	168	341
Median	68·99	54·49	62·17
Range	2·3, 1522·7	10·9, 3169·1	2·3, 3169·1
Ferritin, μg/l			
Median	324·50	253·50	292·50
Range	5·0, 5352·0	15·0, 5027·0	5·0, 5352·0
Transferrin saturation, %			
Median	26·50	25·00	26·00
Range	5·0, 95·0	4·0, 95·0	4·0, 95·0

*Includes Waldenström's macroglobulinaemia.

†Two or more lines of chemotherapy or one line of chemotherapy and a stem cell transplant.

NHL, non-Hodgkin's lymphoma; CLL, chronic lymphocytic leukaemia; ECOG, Eastern Cooperative Oncology Group; EPO, erythropoietin; SD, standard deviation.

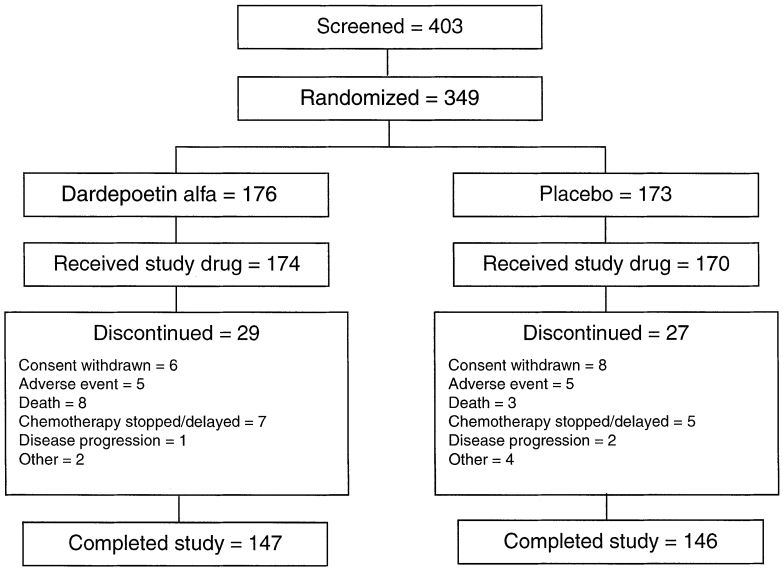

Fig 1. Patient distribution.

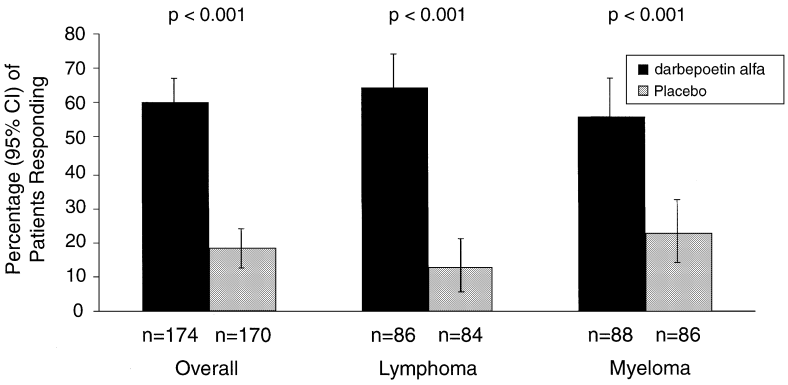

Fig 2. Kaplan–Meier percentages (95% CI) of the patients that achieved a haemoglobin response, according to malignancy type. Haemoglobin response was defined as an increase of ≥2·0 g/dl from baseline in the absence of RBC transfusions within the previous 28 d.

significant difference of 42% (95% CI 32, 52) ($P < 0{\cdot}001$). When the data were analysed by malignancy type, a significant improvement in the rate of haemoglobin response with darbepoetin alfa relative to placebo was observed both in patients with lymphoma (64% *vs* 13%, $P < 0{\cdot}001$) and patients with myeloma (56% *vs* 23%, $P < 0{\cdot}001$).

An exploratory analysis revealed that baseline serum erythropoietin concentration influenced the magnitude of the effect of darbepoetin alfa compared with placebo. For patients with baseline serum erythropoietin levels ≤100 IU/l, 69% (95% CI 60, 79) responded in the darbepoetin alfa group compared with 16% (95% CI 9, 22) in the placebo group. For patients with baseline serum erythropoietin levels >100 IU/l, 44% (95% CI 31, 58) responded in the darbepoetin alfa group and 25% (95% CI 11, 39) responded in the placebo group, indicating that darbepoetin alfa treatment resulted in a 19% (95% CI 0, 38) improvement in haemoglobin response rates compared with placebo in patients with elevated endogenous erythropoietin levels. Thus, darbepoetin alfa demonstrated clinically important improvements in response rate relative to placebo, regardless of baseline endogenous erythropoietin level.

Haematopoietic response. A significantly higher percentage of patients achieved a haematopoietic response (haemoglobin response or a haemoglobin concentration of ≥12·0 g/dl in the absence of any RBC transfusions during the previous 28 d) in the darbepoetin alfa group (65%) than in the placebo group (24%) ($P < 0{\cdot}001$) (Table II).

Change in haemoglobin. The mean (SEM) change in haemoglobin during the study is provided in Table II. In an ITT analysis, the mean (SEM) change in haemoglobin was 1·80 (0·17) g/dl in the darbepoetin alfa group and 0·19 (0·10) g/dl in the placebo group. In an analysis of only those patients who completed at least 12 weeks of treatment (i.e. had a haemoglobin value at week 13 with no transfusions during the preceding 28 d), the mean (SEM) change in haemoglobin was 2·66 (0·20) g/dl in the darbepoetin alfa group and 0·69 (0·14) g/dl in the placebo group.

Effects on red blood cell transfusions

The percentages of patients receiving RBC transfusions during the study according to treatment group are given in Table III. A significantly lower percentage of patients in the

Table II. Haemoglobin endpoints.

	Darbepoetin alfa	Placebo	*P*-value
Haematopoietic response			
n	174	170	
Percentage*	65	24	
(95% CI)	(57, 73)	(18, 31)	< 0·001
Mean change in haemoglobin, g/dl (ITT analysis)†			
n	174	170	
Mean	1·80	0·19	
SE	0·17	0·10	< 0·001
Mean change in haemoglobin, g/dl (completer's analysis)†			
n	94	86	
Mean	2·66	0·69	
SE	0·20	0·14	< 0·001

*Percentage calculated using the Kaplan–Meier estimate.

†Change from baseline calculated using last available haemoglobin value not within 28 d of a transfusion (ITT analysis), and for patients with haemoglobin values at week 13 not within 28 d of a transfusion (completer's analysis).

Table III. Percentage of patients receiving red blood cell transfusions.

	Darbepoetin alfa	Placebo	*P*-value
Transfusions from week 5 to end of treatment			
n	167	165	
Percentage*	31	48	
(95% CI)	(24, 38)	(41, 56)	< 0·001

*Percentage calculated using the Kaplan–Meier estimate.

darbepoetin alfa group received a RBC transfusion during week 5 to the end of treatment than in the placebo group (31% *vs* 48%, $P < 0{\cdot}001$). When the data were analysed within each malignancy type, darbepoetin alfa was associated with a reduction in RBC transfusions compared with placebo both in patients with lymphoma (27% *vs* 49%, $P = 0{\cdot}002$) and patients with myeloma (35% *vs* 48%, $P = 0{\cdot}042$).

When the entire treatment phase (i.e. week 1 to the end of the treatment phase) was considered in the analysis, the percentage of patients receiving RBC transfusions remained significantly lower (17% difference; 95% CI 6, 27) in the darbepoetin alfa group than in the placebo group ($P < 0{\cdot}001$). This reduction in transfusions with darbepoetin alfa compared with placebo was observed both in patients with lymphoma ($P = 0{\cdot}011$) and patients with myeloma ($P = 0{\cdot}018$).

Health-related quality of life

Compliance for the HRQOL questionnaire was high, with 84% of the patients completing the FACT-Fatigue subscale at week 13. Patients treated with darbepoetin alfa showed a greater improvement in their FACT-Fatigue subscale score compared with placebo, regardless of their level of fatigue at baseline (Fig 3). However, those patients with the lowest baseline FACT-Fatigue subscale scores reported the largest improvement in FACT-Fatigue subscale score at the end of treatment. After adjusting for the effect of baseline score, increases in FACT-Fatigue subscale scores with darbepoetin alfa treatment were significantly greater than those observed with placebo ($P = 0{\cdot}032$). In addition, a statistically significant ($P < 0{\cdot}001$) relationship between change in haemoglobin and change in FACT-Fatigue over the treatment period was found. For every 1 g/dl increase in haemoglobin, the estimated mean increase in FACT-Fatigue subscale score was 1·39 (95% CI 0·83, 1·94).

Safety

In general, the safety profiles of darbepoetin alfa and placebo were consistent with that generally associated with malignant disease and the toxic effects of chemotherapy. Figure 4 shows the incidence of adverse events that occurred in at least 15% of patients in either treatment group. The most frequently reported adverse events were fatigue, fever and nausea. No relationship was observed between the incidence of hypertension or thrombotic events and high or increasing haemoglobin concentrations.

Ten patients (6%) in the darbepoetin alfa group and four patients (2%) in the placebo group died during the study or within 30 d after the last dose of study drug. Most deaths were attributed to progressive disease, and none were considered to be related to the study drug by the investigators. The incidence of withdrawal from the study as a result of adverse events (other than death) was similar for the darbepoetin alfa (3%) and placebo (4%) groups.

The percentage of patients receiving iron supplementation during the study was similar between treatment groups for oral (6% darbepoetin alfa, 7% placebo) and intravenous (0% darbepoetin alfa, 1% placebo) iron-containing medications.

An initial analysis of long-term data on disease status and survival was conducted after a median follow-up period of approximately 11 months. During the combined study period and follow-up period, the incidence of disease progression or death (i.e. progression-free survival) was similar in the darbepoetin alfa group (82 patients, 47%) and the placebo group (76 patients, 45%).

No evidence of neutralizing antibodies to darbepoetin alfa was detected for any patient.

DISCUSSION

The results of this multicentre, randomized, double-blind, placebo-controlled study demonstrated that darbepoetin alfa was an effective and well-tolerated treatment for chemotherapy-induced anaemia in patients with lymphoproliferative malignancies. A significantly higher percentage of patients achieved the primary endpoint, a haemoglobin response, in the darbepoetin alfa group (60%) than in the placebo group (18%) ($P < 0{\cdot}001$). Similarly, darbepoetin alfa was associated with a significantly higher rate of

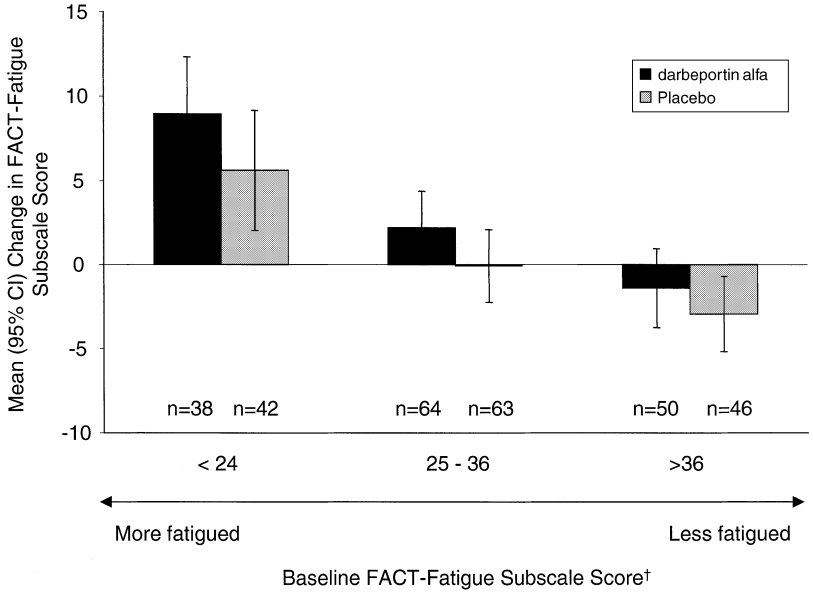

Fig 3. Change in FACT-Fatigue subscale score* by baseline FACT-Fatigue subscale score. *13 items, range: 0–52. †Categorization of the continuous FACT-Fatigue subscale scores derived from Cella *et al* (2002).

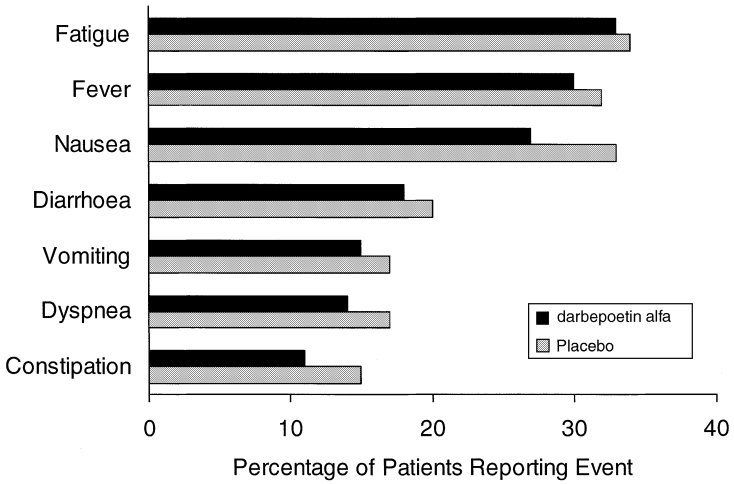

Fig 4. Adverse events that occurred in at least 15% of patients receiving darbepoetin alfa ($n = 175$) or placebo ($n = 169$).

haematopoietic response compared with the placebo group (65% *vs* 24%, $P < 0{\cdot}001$). The mean change in haemoglobin from baseline to the last value during the treatment phase in patients receiving darbepoetin alfa was 1·80 g/dl based on an ITT analysis; the mean change for patients completing 12 weeks of treatment was 2·66 g/dl. These endpoints have been commonly used as measurements of efficacy in previously published studies of erythropoietic agents (Abels *et al*, 1991; Glaspy *et al*, 1997; Dammacco *et al*, 2001; Gabrilove *et al*, 2001; Littlewood *et al*, 2001; Vansteenkiste *et al*, 2002). In previously published studies of epoetin in patients with lymphoproliferative malignancies, typical haemoglobin response rates of approximately 50% have been reported, although some differences based on the duration of treatment, dosing criteria and eligibility parameters have been observed between studies (Cazzola *et al*, 1995; Österborg *et al*, 1996, 2002; Dammacco *et al*, 2001).

In this study, a significant reduction in the percentage of patients requiring a RBC transfusion from week 5 to the end of the treatment phase was observed for patients receiving darbepoetin alfa (31%) compared with those receiving placebo (48%) ($P < 0{\cdot}001$). Typically, a reduction in RBC transfusions in patients receiving epoetin is not apparent until after the first month of treatment (Abels *et al*, 1991; Dammacco *et al*, 2001; Littlewood *et al*, 2001), probably reflecting the kinetics of epoetin-stimulated erythropoiesis and the time required to produce a sufficient quantity of RBC to affect the need for transfusion. However, darbepoetin alfa was associated with a significant ($P < 0{\cdot}001$) reduction in RBC transfusions even when data from the first 4 weeks of treatment were included in the analysis. This overall effect on RBC transfusions has also been observed in a previous study of darbepoetin alfa conducted in patients with lung cancer (Vansteenkiste *et al*, 2002).

Previous studies of erythropoietic agents have suggested that haemoglobin response rates may differ between patients with multiple myeloma and those with other types of lymphoproliferative malignancies (Österborg *et al*, 1996; Dammacco *et al*, 1998). However, a large, randomized, placebo-controlled study conducted in patients with multiple myeloma did not report higher response rates than those expected for other lymphoproliferative malignancies (Dammacco *et al*, 2001), and a more recent study reported similar haemoglobin response rates between patients with multiple myeloma, non-Hodgkin's lymphoma or chronic lymphocytic leukaemia (Österborg *et al*, 2002). To investigate this potential effect, the current study was designed to evaluate the treatment effect of darbepoetin alfa relative to placebo separately for patients with lymphoma (Hodgkin's disease, non-Hodgkin's lymphoma or chronic lymphocytic leukaemia) or myeloma. The significant increase in haemoglobin response and reduction of RBC transfusions with darbepoetin alfa relative to placebo were observed consistently in patients with lymphoma or with myeloma, indicating that patients with either malignancy type benefited from darbepoetin alfa treatment.

Baseline endogenous serum erythropoietin has previously been identified as a potential factor to predict responsiveness to erythropoietic therapy in patients with lymphoproliferative malignancies, with a higher likelihood of response for those patients with an absolute or relative erythropoietin deficiency (Ludwig *et al*, 1990; Barlogie & Beck, 1993; Cazzola *et al*, 1995; Österborg *et al*, 1996). Although no definitive threshold for endogenous erythropoietin has been established, a recent study of epoetin (Österborg *et al*, 2002) defined a relative erythropoietin deficiency as a level ≤ 100 IU/l for patients with a haemoglobin concentration between 9 and 10 g/dl. In an analysis of the effect of baseline serum erythropoietin (≤ 100 IU/l *vs* > 100 IU/l) on haemoglobin response in patients receiving darbepoetin alfa or placebo in the present study, the treatment effect of darbepoetin alfa relative to placebo was evident regardless of baseline endogenous erythropoietin level, although an increased effect was observed in patients with values ≤ 100 IU/l.

Current clinical practice guidelines have noted an absence of confirmatory evidence concerning the quality-of-life benefits of epoetin in large, well-designed clinical trials (Rizzo *et al*, 2002). This randomized, double-blind study provides evidence that treatment with darbepoetin alfa alleviates patient-reported fatigue, with clinically meaningful improvements for those patients who are most fatigued (Cella *et al*, 2002). The mitigation of fatigue is associated with many beneficial outcomes for patients, including reductions in depression and anxiety (Kallich *et al*, 2002), improvements in productivity, and a reduction in the amount of carer time required (Berndt *et al*, 2002).

The safety profile of darbepoetin alfa in this study was similar to that of placebo, and consistent with adverse events generally associated with malignant disease and the toxic effects of chemotherapy. No evidence of neutralizing antibodies to darbepoetin alfa was detected for any patient. Furthermore, an analysis of long-term follow-up information collected over approximately 1 year did not reveal any increased risk of tumour stimulation with darbepoetin alfa treatment.

In conclusion, darbepoetin alfa is effective and well tolerated for the treatment of anaemia in patients with lymphoproliferative malignancies who are receiving chemotherapy, resulting in improvements in haemoglobin, a decreased need for RBC transfusions and relief from the anaemia-associated symptoms of fatigue. The results of this study demonstrated that darbepoetin alfa was beneficial across a broad population of patients with lymphoproliferative malignancies, although an increased responsiveness in the subset of patients with low erythropoietin levels was observed. Given the longer half-life of darbepoetin alfa relative to epoetin, the investigation of less-frequent dosing schedules for the treatment of anaemia in this population is warranted.

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Additional members of the darbepoetin alfa 20000161 Study Group include the following individuals:

Dr Chris Arthur, Royal North Shore Hospital, St Leonards, NSW, Australia

Dr John Bashford, Wesley Medical Centre, Auchenflower, Qld, Australia

Dr Robert Belanger, Hôpital Maisonneuve-Rosemont, Montreal, Canada

Professor Dr M. Boogaerts, UZ Gasthuisberg, Leuven, Belgium

Professor A. Bosly, UCL CU de Mont Godinne, Yvoir, Belgium

Dr Rena Buckstein, Toronto Sunnybrook Regional Cancer Centre, Toronto, Canada

Dr Ian Chin-Yee, London Health Sciences Centre, London, Canada

Dr Stephen Couban, Queen Elizabeth II Health Sciences Centre, Halifax, Canada

Dr Jorge Coutinho, Hospital Geral de Santo António, Porto, Portugal

Professor Giorgio Lambertenghi Deliliers, Maggiore Hospital of Milan – IRCCS, Milano, Italy

Professor Dr med Hartmut Döhner, Universitätsklinikum Ulm, Ulm, Germany

Professor Dr med Berthold Emmerich, Medizinische Klinik der Universität München, Standort Innenstadt, München, Germany

Professor Eugenio Gallo, Ospedale S Giovanni – Sede Molinette, Torino, Italy

Professor Javier García-Conde, Hospital Clínico Universitario de Valencia, Valencia, Spain

Dr Malcolm Green, Ashford Cancer Centre, Ashford, Australia

Dr Mads Hansen, Rigshospitalet, Copenhagen, Denmark

Dr Soren Hansen, Hoglandssjukhuset, Eksjo, Sweden

Dr Richard Herrmann, Royal Perth Hospital, Perth, WA, Australia

Professor Wolfgang Hiddemann, Klinikum der Universität München Großhadern, München, Germany

Dr Hans Johnsen, Herlev Hospital, Herlev, Denmark

Dr Elli Koivunen, Tampere University Hospital, Tampere, Finland

Dr Elisabeth Koller, Hanusch Krankenhaus, Wien, Austria

Dr Dusan Kotasek, Ashford Cancer Centre, Ashford, Australia

Professor João F. Lacerda, Hospital de Santa Maria, Lisboa, Portugal

Dr Juan José Lahuerta, Hospital 12 de Octubre, Madrid, Spain

Dr Birgitta Lauri, Sunderby Hospital, Luleaa, Sweden

University Professor Dr Klaus Lechner, Universitätsklinik für Innere Medizin I, Wien, Austria

University Professor Dr Werner Linkesch, Medizinische Universitätsklinik Graz, Graz, Austria

Dr Jeanette Lundin, Karolinska Hospital, Stockholm, Sweden

Professor Anna Teresa Maiolo, Maggiore Hospital of Milan– IRCCS, Milano, Italy

Dr Donald W. Milligan, Birmingham Heartlands Hospital, Birmingham, UK

Professor Enrica Morra, Niguarda Ca Granda Hospital, Milano, Italy

Professor Dr Luc Noens, UZ Gent, Gent, Belgium

Dr Inês Nolasco, Instituto Portugues de Oncologia Francisco Gentil – Centro de Lisboa, Lisboa, Portugal

Professor Nigel Russell, Nottingham City Hospital, Nottingham, UK

Dr A Keith Stewart, Princess Margaret Hospital, Toronto, Canada

Professor Sante Tura, Policlinico S. Orsola – Institute 'Seragnoli', Bologna, Italy

Dr Craig Underhill, Murray Valley Private Hospital, Wodonga, Australia

Dr L. F. Verdonck, Universitair Medisch Centrum, Utrecht, Netherlands

Dr C. Williams, Christie Hospital, Manchester, UK.

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