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Darbepoetin alfa administered every 3 weeks alleviates anaemia in patients with solid tumours receiving chemotherapy; results of a double-blind, placebo-controlled, randomised study

D. Kotasek[a,*], G. Steger[b], W. Faught[c], C. Underhill[d], E. Poulsen[e], A.B. Colowick[e], G. Rossi[e], J. Mackey[f] for the Aranesp™ 980291 Study Group

[a]*Ashford Cancer Centre, 15 Alexander Avenue, Ashford SA 5035, Australia*
[b]*Division of Oncology, UnivKlinik für Innere Medizin I, Klinische Abteilung für Onkologie; Währinger Gürtel 18–20, Wien, Austria*
[c]*The Ottawa Hopital, General Division; 501 Smyth Road, Ottawa, Ontario, Canada K1H 8L6*
[d]*Border Medical Oncology, Murray Valley Private Hospital; Nordsvan Drive, Wodonga VIC 3690, Australia*
[e]*Amgen Inc., One Amgen Center Drive; M/S 24-1-C; Thousand Oaks, CA 91320, USA*
[f]*Cross Cancer Institute, 11560 University Ave., Edmonton, Alberta (AB) Canada T6G 1Z2*

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Abstract

This dose-finding, placebo-controlled study evaluated the safety and efficacy of darbepoetin alfa administered every 3 weeks (Q3W) to anaemic patients receiving chemotherapy. In part A, patients (haemoglobin $\leqslant$110 g/l) were randomised in a 1:4 ratio to receive 1 of 6 doses of darbepoetin alfa (4.5, 6.75, 9.0, 12.0, 13.5 and 15.0 μg/kg) or placebo Q3W for 12 weeks. In part B, patients received open-label darbepoetin alfa. Patients ($n=249$) were evaluated for safety, haemoglobin endpoints and red blood cell (RBC) transfusions. Darbepoetin alfa given at doses ranging from 4.5 to 15.0 μg/kg Q3W was well tolerated and comparable to placebo in terms of safety. No neutralising antibodies were detected. All doses (from 4.5 to 15 μg/kg) reduced transfusions compared with placebo, and resulted in >50% of patients achieving a haematopoietic response. Administration of darbepoetin alfa Q3W has a tolerable safety profile and effectively ameliorates anaemia due to chemotherapy.

Keywords: Anaemia; Chemotherapy-induced anaemia; Darbepoetin alfa; Erythropoietin; Haemoglobin

1. Introduction

Anaemia is a common side-effect in many patients with cancer receiving chemotherapy and contributes to the fatigue experienced by these patients [1–4]. Recombinant human erythropoietin is effective in relieving anaemia in this setting [2–4,5–7]. Approximately 40–60% of patients in these studies achieved a haemoglobin increase of at least 20 g/l, and improvements in clinical outcomes (transfusion requirements and quality-of-life measures) were demonstrated.

Despite the rationale for the use of erythropoietic therapy for cancer-related anaemia, anaemic patients frequently do not receive this treatment until their haemoglobin level has dropped as low as 90 g/l [8]. Factors that may contribute to the current low rate of treatment include the cost of therapy, the lack of perception of the importance of anaemia by treating physicians, the indicated administration schedule of 3 times per week (TIW), and the relatively high degree of non response to therapy.

A recent study demonstrated the effectiveness of once-weekly (QW) dosing of recombinant human erythropoietin, although at this schedule a 33% increase in dose was required compared with the registered dosing recommendations of TIW administration [4]. These results have led to the adoption of a QW schedule in many community practices in the United States. Further reductions in dosing frequency would be desirable, particularly if an erythropoietic

* Corresponding author. Tel.: +61-8-8351-0211; fax: +61-8-8351-0255.
E-mail address: dusan.kotasek@bigpond.com (D. Kotasek).

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agent could be administered at the same schedule as many common chemotherapy regimens (e.g., Q3W).

Darbepoetin alfa stimulates erythropoiesis by the same mechanism as endogenous erythropoietin and recombinant human erythropoietin through binding to the erythropoietin receptor [9]. However, darbepoetin alfa has 2 additional carbohydrate side chains, which result in an extended residence time and a consequential increase in potency compared with recombinant human erythropoietin [9].

We report the results of a large, international, randomised, double-blind, placebo-controlled, dose-finding study of darbepoetin alfa given subcutaneously (s.c.) Q3W to patients with cancer receiving chemotherapy. The purpose of the study was to assess the safety of darbepoetin alfa in patients receiving chemotherapy, to assess the feasibility of administering darbepoetin alfa Q3W, and to characterise the dose–response relationships for darbepoetin alfa when given Q3W.

2. Patients and methods

2.1. Study population

The independent ethics committee or central ethics committee for each of the 26 participating centres in Australia, Canada, Costa Rica, and Europe approved the protocol and all patients gave written informed consent before any study-specific procedures were done. Patients who were $\geqslant 18$ years of age with solid tumours and were receiving cyclic chemotherapy were eligible for this study if they had a $\geqslant 6$-month life expectancy, an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, and adequate renal and liver function. Patients were required to have anaemia (haemoglobin concentration $\leqslant 110$ g/l), predominantly due to cancer and/or chemotherapy.

Patients who were iron-deficient (transferrin saturation $<15\%$ and ferritin <10 μg/l), or who had received recombinant human erythropoietin within 8 weeks before randomisation, >2 red blood cell transfusions within 4 weeks of randomisation, or any red blood cell transfusion within 2 weeks of randomisation were excluded from the study. Other exclusion criteria included known primary haematological disorders that could cause anaemia and central nervous system, cardiac, or inflammatory diseases.

2.2. Study drug

Darbepoetin alfa (Aranesp®, Amgen Inc., Thousand Oaks, California) was supplied in vials as a clear, colourless, sterile protein containing 500, 1000, or 1500 μg darbepoetin alfa per ml. Placebo was supplied in identical vials.

2.3. Study design

This was a two-part, multicentre, international, randomised, double-blind, placebo-controlled study (Fig. 1). In part A, anaemic patients with solid tumours who were receiving chemotherapy had up to 12 weeks of s.c. therapy with darbepoetin alfa or placebo. Patients were randomised in a 4:1 ratio to receive darbepoetin alfa (4.5, 6.75, 9.0 or 13.5 μg/kg) or placebo, administered Q3W. Later, after review of data by the safety monitoring committee, darbepoetin alfa dose cohorts of 12.0 and 15.0 μg/kg were added. In part B, patients who had completed part A and were continuing to receive multicycle chemotherapy had the option of receiving open-label darbepoetin alfa for up to 12 additional weeks.

No dose increase for inadequate initial response was allowed in part A of this study. The study drug was withheld if a patient's haemoglobin value increased to >150 g/l for men or >140 g/l for women. Once the haemoglobin value was $\leqslant 130$ g/l, the study drug could be reinstated at a lower dose level.

Trough and 48-h serum samples for the determination of darbepoetin alfa concentration were collected at weeks 1, 4 and 10 of part A. Quality-of-life assessments were done at weeks 1, 4, 7 and 10. The quality-of-life evaluation in this study was designed to assess the feasibility, reliability, validity, sensitivity and timing of quality-of-life surveys in this setting, rather than to evaluate fatigue.

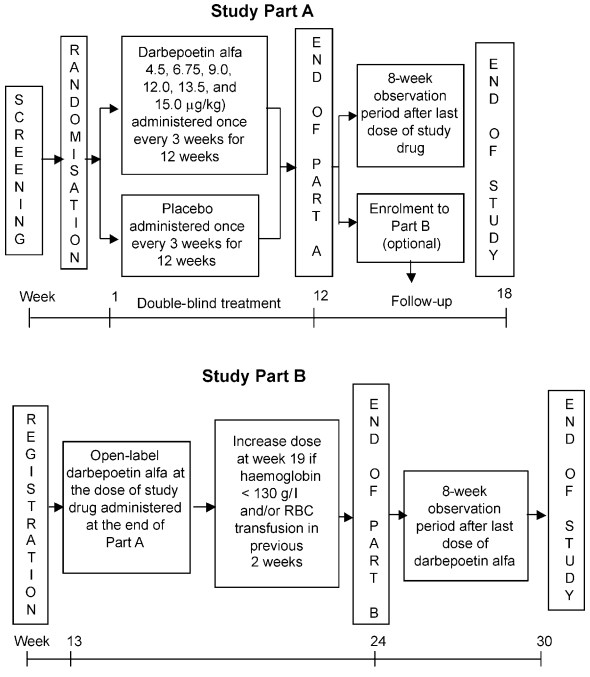

Fig. 1. Study design. Panel A, part A; panel B, part B. RBC, red blood cell.

2.4. Study endpoints

The primary objective of this study was to assess the safety of darbepoetin alfa administered to anaemic patients receiving cancer chemotherapy. Safety was assessed in both part A and part B by summarising the incidence of adverse events by dose and treatment group and evaluating the formation of antibodies resulting from the darbepoetin alfa administration. Two validated assays were used to evaluate antibody formation: a radioimmunoprecipitation screening assay to detect seroreactivity to darbepoetin alfa and a cell-based bioassay to detect neutralising or inhibiting effects on the activity of darbepoetin alfa.

Other endpoints included evaluation in part A of the potential efficacy of darbepoetin alfa, assessed by the incidence of patients who achieved a haemoglobin response (defined as an increase in haemoglobin of $\geqslant 20$ g/l from baseline during the 12-week treatment phase, in the absence of any red blood cell transfusions in the previous 28 days); the incidence of patients with a haematopoietic response, defined as a haemoglobin response and/or haemoglobin concentration $\geqslant 120$ g/l during the treatment phase in the absence of any red blood cell transfusions in the previous 28 days; change in haemoglobin from baseline during treatment; and the incidence of red blood cell transfusions. We assessed the feasibility, reliability, validity, sensitivity and timing of quality-of-life surveys in this setting by administering a quality-of-life survey questionnaire which included the Functional Assessment of Cancer Therapy FACT-An, which contains the FACT-General 4 subscales and the FACT-Fatigue Subscale. Darbepoetin alfa concentration was determined from serum samples taken pre-dose and 48 h post-dose on weeks 1, 4 and 10 of part A.

2.5. Statistical analysis

The sizing of this dose-finding study supported the primary objective of the study, assessing safety, by providing an early evaluation of short-term safety and tolerability. The sample size was statistically based on the secondary objective of the study, to determine a clinically effective dose, by means of estimating haemoglobin response rates. Specifically, the 4:1 randomisation ratio allowed for approximately 36 darbepoetin alfa subjects per dose cohort. With an anticipated premature withdrawal rate of approximately 20%, a sample size of 29 allows estimation of the true haemoglobin response rate within a standard error of approximately 0.09 (using the formula $[pq/n]^{1/2}$, where $p = q = 0.50$). The exact number of subjects in each cohort was ultimately determined by the rate of enrolment and how long it took the data monitoring committee to determine safety in each cohort before allowing dose escalation.

Statistical analyses were conducted on patients randomised to study drug who received at least one dose. Baseline demographic and clinical characteristics were summarised by the mean and standard deviation (SD) for continuous measures and number and percentage for categorical measures. All adverse events were classified using a modified World Health Organization (WHO) adverse reaction term dictionary, and the number (%) of patients experiencing adverse events was tabulated. The number (%) of patients with antibodies resulting from darbepoetin alfa administration was summarised.

The proportions of patients in each dose group were calculated for haemoglobin response, haematopoietic response, and incidence of red blood cell transfusions from week 5 to the end of the treatment phase. The proportion was estimated by taking 1 minus the Kaplan–Meier estimate of the survivor function at the time of the last observed endpoint (the Kaplan–Meier estimate). Approximate 95% confidence intervals (CIs) for the Kaplan–Meier estimate of the proportion were calculated using Greenwood's [10] estimate of the variance and assuming a normal distribution for the Kaplan–Meier estimate. The time to haematopoietic response was determined.

For the analysis of the incidence of red blood cell transfusions, a subset of the analysis set was used. Because other studies evaluating transfusion requirements have suggested that observable treatment effects are not expected until after 4 weeks of treatment [6,7,11], we analysed the incidence of red blood cell transfusions from week 5 to the end of the treatment phase on a subset of patients consisting of all properly consented patients who received at least one dose of study drug and who ended their treatment phase during week 5 or later. Patients who had more than one transfusion were counted only once in calculating the incidence of transfusions.

The change in haemoglobin concentration from baseline was assessed by two methods. Change in haemoglobin from baseline to the end of the treatment phase was calculated for each patient as the end-of-treatment-phase haemoglobin value minus the baseline value. If a patient had a red blood cell transfusion within 28 days of the last treatment-phase haemoglobin value, then the last pretransfusion haemoglobin value was substituted to discount the effect of the red blood cell transfusion on the change in haemoglobin. All patients had an observed or imputed value for this analysis as patients who withdrew after one dose of study drug with no treatment-phase haemoglobin value were given a change score of zero. Change in haemoglobin was also analysed using the set of patients who completed at least 12 weeks of treatment. For change in haemoglobin the mean and standard error (SE) were calculated.

In order to further examine the dose relationship of darbepoetin alfa, analyses were also done for mean change in haemoglobin at the end of the treatment phase across increasing dose groups, and mean change in FACT-Fatigue across categorised change in haemoglobin (the change in haemoglobin at a patient's last available quality-of-life assessment was used in the analysis of FACT-Fatigue). These analyses were not specified in the protocol. In each case, a trend test was conducted using a distribution-free test. Asymptotic *P*-values were obtained using the 2-sided Jonckheere–Terpstra test.

3. Results

3.1. Patient demographics and disposition

A total of 249 patients received at least one dose of study drug (198 darbepoetin alfa and 51 placebo). In general, baseline demographic and clinical characteristics of patients were well balanced between the darbepoetin alfa and placebo groups (Table 1). A slightly higher proportion of patients in the 12.0-μg/kg group had breast cancer (61%) compared with the other groups, which ranged from 15 to 38%. The 12.0-μg/kg group also had a slightly higher mean baseline haemoglobin concentration (104 g/l) compared with mean concentrations between 97 and 102 g/l for the other groups. No clinically meaningful differences in pretreatment chemotherapy were seen between the darbepoetin alfa and placebo patients (data not shown).

The disposition of patients enrolled into the trial is given in Fig. 2. 138 patients (70%) receiving darbepoetin alfa and 37 patients (73%) receiving placebo completed part A of the study. The reasons for withdrawal were primarily delay or discontinuation of chemotherapy, withdrawal of consent, or death. 119 patients enrolled into part B of the study and 112 received open-label darbepoetin alfa. 10 patients (4.0%) died during part A and 12 (10.1%) died during part B; the incidences of death, disease progression, and delay or discontinuation of chemotherapy are as expected for this patient population. The mean administered number of darbepoetin alfa doses over the 12-week treatment phase was 3.6.

3.2. Safety

The adverse events reported were comparable between the darbepoetin alfa and placebo patients and generally consistent with those expected for patients being treated with myelosuppressive chemotherapy. The

Table 1
Baseline demographic and clinical characteristics (shown by dose) at the start of part A were similar between the two treatment groups

	Placebo *N* = 51	Darbepoetin alfa (μg/kg/3 weeks) *N* = 198
Age (years)		
Mean (S.D.)	56.2 (12.4)	58.3 (11.9)
Sex (*n*/%)		
Women	35 (69)	142 (72)
Disease (*n*/%)		
Breast	13 (25)	61 (31)
Gynaecological	9 (18)	46 (23)
Gastrointestinal	13 (25)	34 (17)
Lung	10 (20)	33 (17)
Other	6 (12)	24 (12)
ECOG status (*n*/%)		
<2	45 (88)	180 (91)
Haemoglobin (g/l)		
Mean (S.D.)	98.7 (11.2)	99.3 (10.0)
Endogenous EPO (patients with ⩾100 mU/ml)		
N	47	183
n/%	7 (15)	32 (17)
Ferritin (μg/l) (*n*/%)		
<50	3 (6)	21 (11)
Mean (S.D.) FACT-F Score (quality-of-life population [*n* = 239]; darbepoetin alfa and placebo combined).	27.2 (12.4)	

S.D., standard deviation; FACT-F, Functional Assessment of Cancer Therapy—Fatigue; ECOG, Eastern Cooperative Oncology Group; EPO, erythropoietin; N, number of patients in group; n, number with characteristic.

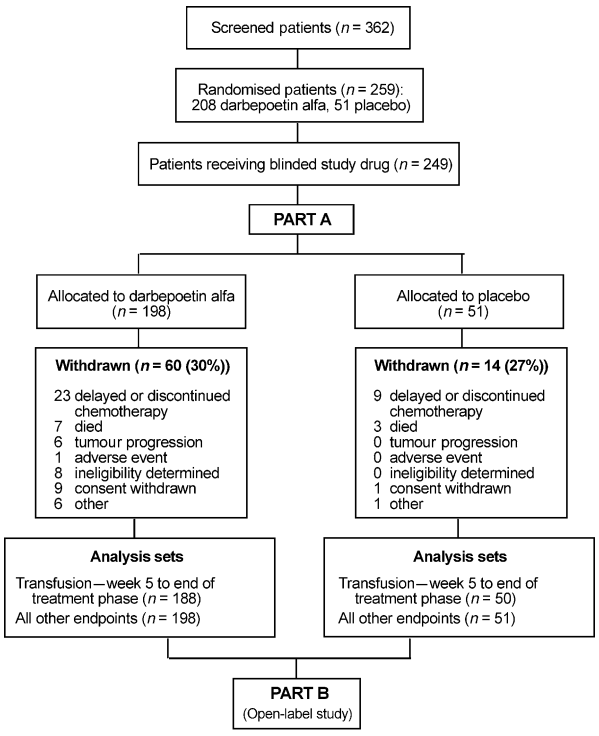

Fig. 2. Patient disposition. Other category includes: 1 patient with disease progression who chose another clinical trial, 1 on vacation, 2 lost to follow-up, 1 with protocol violation, 1 with non-compliance, and 1 who discontinued due to an administrative decision.

most frequently reported adverse events in part A were nausea, fatigue and vomiting (Fig. 3). In general, the findings in part B did not deviate from the safety profile in part A. No relationship between the dose and adverse events was noted.

15 patients reached the maximum haemoglobin concentration, and of these, five had the study drug withheld according to the protocol. (4 patients had completed the study drug administration at the time of their maximum haemoglobin concentration, and in six patients, the study drug was not withheld according to protocol). In general, when therapy was withheld, haemoglobin levels decreased or stabilised in a predictable and controllable manner (Fig. 4).

No neutralising antibodies to darbepoetin alfa were detected.

3.3. Pharmacokinetics

Analysis of serum samples collected weeks 1, 4 and 10 of part A revealed no consistent increase in the mean concentration of darbepoetin alfa over time (Fig. 5).

3.4. Efficacy endpoints

A dose–response relationship was noted in the percentage of patients achieving a haemoglobin response, with response rates ranging from 24% (95% CIs = 8–39) in the 4.5-μg/kg group to 62% (95% CIs = 41–82) in the 12-μg/kg group, compared with 14% (95% CIs = 3–24) in the placebo group (Fig. 6). No additional increase in the percentage of patients achieving a haemoglobin response was seen with doses greater than 12 μg/kg Q3W.

As with the haemoglobin response, the percentage of patients achieving a haematopoietic response indicated a dose-response relationship, with the highest response rate being observed in the 12.0-μg/kg group (71% [95%

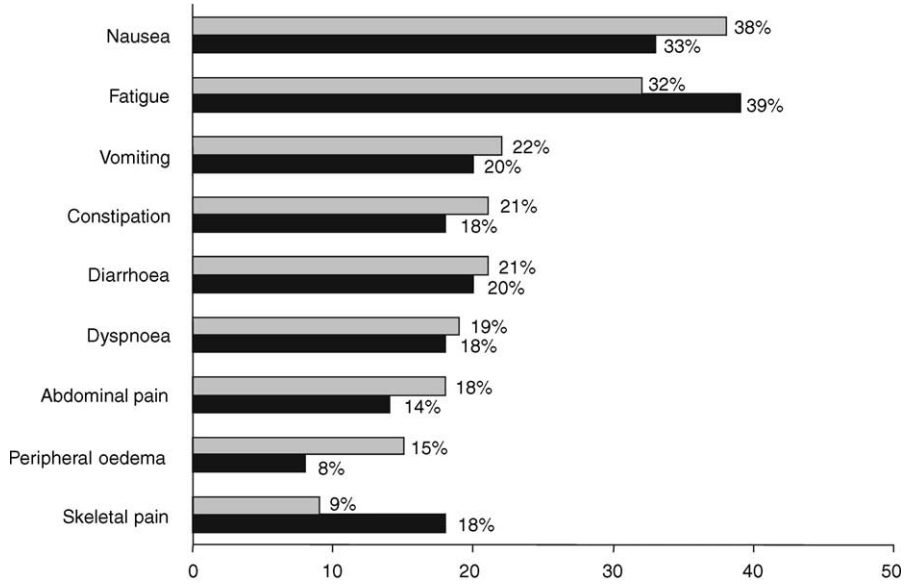

Fig. 3. Adverse events that occurred with ⩾15% incidence in patients receiving darbepoetin alfa or placebo. Grey bars, darbepoetin alfa ($n = 198$); solid bars, placebo ($n = 51$).

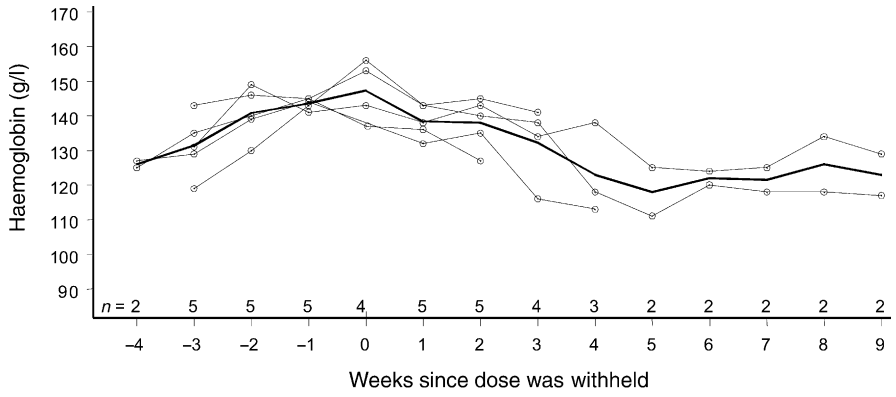

Fig. 4. Changes in haemoglobin after the dose was withheld for patients receiving darbepoetin alfa. Individual patients are shown. Week 0 is the week the dose was first withheld. The bold line connects the weekly mean haemoglobin concentration for subjects who had a dose withheld.

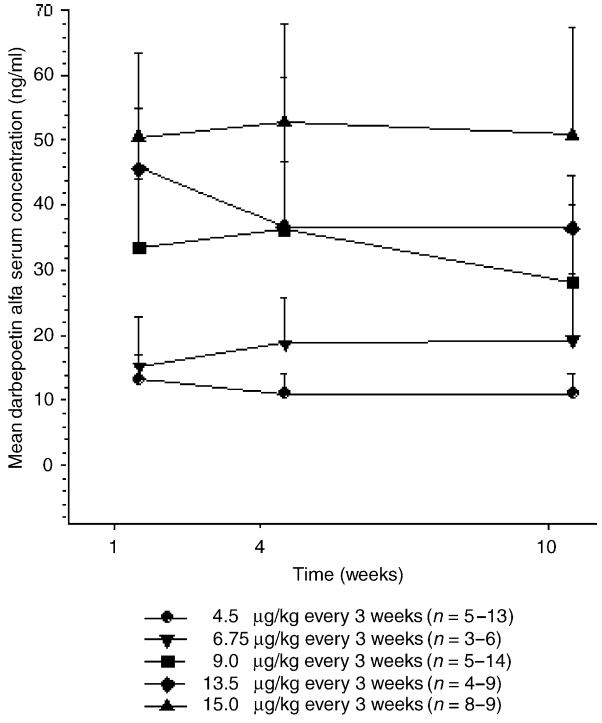

Fig. 5. Darbepoetin alfa concentrations in the serum at weeks 1, 4 and 10 of part A of the study. Bars represent the standard deviation. The 12.0-µg/kg dose cohort is not included due to insufficient data.

CIs: 52–91]). Again, no additional increase was seen in the percentage of patients achieving a response at higher doses (Table 2). Generally, a trend towards a more rapid response with higher doses was evident (data not shown).

While the haemoglobin response rate in the 4.5-µg/kg group (the lowest of the doses studied) was 24%, a substantial proportion of patients had a haematopoietic response at this dose (51% [95% CIs: 33–70]), indicating that clinically meaningful erythropoiesis was evident.

In general, the mean change in haemoglobin increased with increasing darbepoetin alfa dose (Table 2) ($P = 0.01$). No additional benefit was observed beyond 12.0 µg/kg, suggesting a dose response threshold at this level. After 12 weeks of therapy, changes in haemoglobin concentration of approximately $\geqslant 10$ g/l were observed at doses of 6.75 µg/kg and greater (Table 2).

A lower percentage of patients in the darbepoetin alfa groups required red blood cell transfusions from week 5 to the end of the treatment phase compared with patients receiving placebo (46% [95% CIs: 32–61]) (Fig. 7). No differences between the darbepoetin alfa groups could be observed; transfusion rates varied from 19% [95% CIs: 6–32] to 30% [95% CIs: 16–44], with 25% [95% CIs: 9–41] of patients in the 4.5-µg/kg darbepoetin alfa group requiring red blood cell transfusions from week 5 to the end of the treatment phase.

The change in the health-related quality-of-life FACT-Fatigue score from baseline to the end of the treatment phase by change in haemoglobin is shown in Fig. 8. The mean baseline FACT-Fatigue score for all patients was 27.2 (out of a possible maximum of 52 points in the FACT-Fatigue scale) (Table 1), comparable to the mean of 23.9 considered normal for anaemic cancer patients, and lower than that for non-anaemic cancer patients (40.0) or the general population (43.6) [12]. In general, the mean change in FACT-Fatigue score appears to increase with increasing haemoglobin concentration, from roughly no change in patients who had no improvement in their haemoglobin, to an approximately 5-point improvement in patients whose haemoglobin increased by greater than 20 g/l. A trend test of the relationship between the FACT-Fatigue score and haemoglobin concentration was significant at a level of $P = 0.0023$.

4. Discussion

The prolonged half-life of darbepoetin alfa compared with recombinant human erythropoietin suggested that it might be possible to administer darbepoetin alfa

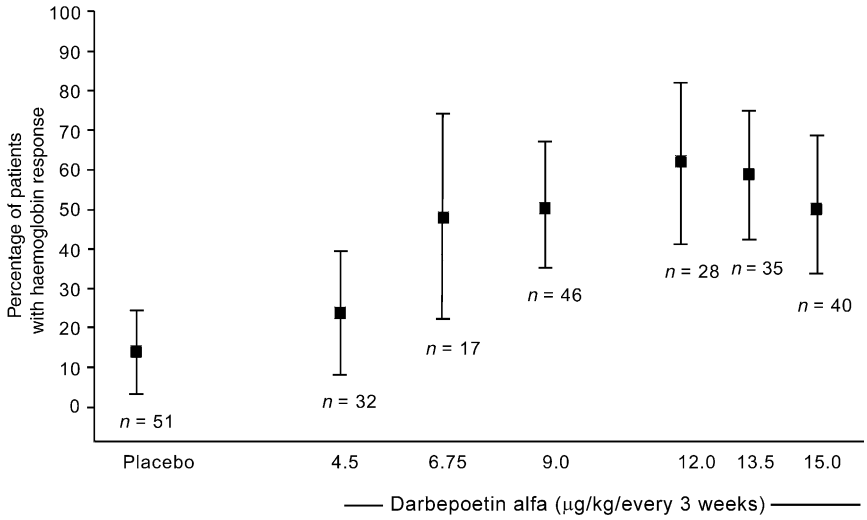

Fig. 6. Haemoglobin response with darbepoetin alfa appears to be dose-dependent. Kaplan–Meier proportion shown. Bars represent 95% confidence intervals (CIs).

Table 2
Haematopoietic response and change in haemoglobin. Haemoglobin values within 28 days of a red blood cell transfusion have been omitted

		Darbepoetin alfa dose (μg/kg/every 3 weeks)					
	Placebo $N=51$	4.5 $N=32$	6.75 $N=17$	9.0 $N=46$	12.0 $N=28$	13.5 $N=35$	15.0 $N=40$
No. with response							
K-M proportion (95% CI)	31 (16–45)	51 (33–70)	52 (27–78)	61 (45–77)	71 (52–91)	64 (48–81)	58 (42–74)
Change in hgb from baseline to the end of the treatment phase (g/l)							
Mean	−0.2	5.4	8.6	9.0	16.3	14.5	12.1
S.E.	2.0	2.2	3.8	2.4	3.8	2.4	3.0
Change in hgb from baseline after 12 weeks (g/l)[a]							
N	37	25	11	34	20	32	29
Mean	3.1	7.0	10.2	9.7	22.5	15.0	14.2
S.E.	2.4	2.8	5.4	2.5	3.9	2.7	3.9

hgb, haemoglobin; CI, confidence interval; S.E., standard error; *N*, number of patients in group; K-M, Kaplan–Meier.

[a] For the analysis of haemoglobin change after 12 weeks, a window was used allowing week 12 or 14 to be used in the absence of an evaluable week-13 haemoglobin value.

Q3W, coinciding with the schedule of administration for many of the common chemotherapy regimens. The present study was undertaken to assess the feasibility of Q3W dosing with darbepoetin alfa in anaemic patients undergoing chemotherapy for solid tumours. To better characterise the relationship of dose to the safety and efficacy of darbepoetin alfa at this schedule of administration, patients' doses were not increased for an inadequate initial response.

Whether measured using the haemoglobin-based or transfusion endpoints, dosing of darbepoetin alfa Q3W was effective in these patients. At the 6.75-μg/kg dose, the proportion of patients achieving a haemoglobin response and haematopoietic response was approximately 50% in each case. In general, higher doses elicited higher response rates for the haemoglobin endpoints, with an increase from the 4.5-μg/kg group through to the 12.0-μg/kg dose group. However, for transfusion-based endpoints, no dose response was observed.

In the 4.5-μg/kg group, 51% of patients achieved a haematopoietic response ($\geqslant$20 g/l haemoglobin increase and/or haemoglobin concentration $\geqslant$120 g/l). This suggests that for many patients receiving the lowest dose of darbepoetin alfa tested in this study, haemoglobin levels were stabilised during the 12-week treatment phase though a 20 g/l increase was not achieved in all these patients. While the study was not designed to formally compare individual dose groups with placebo, the 4.5-μg/kg group appeared to benefit from a reduction in transfusion requirements compared with patients given placebo.

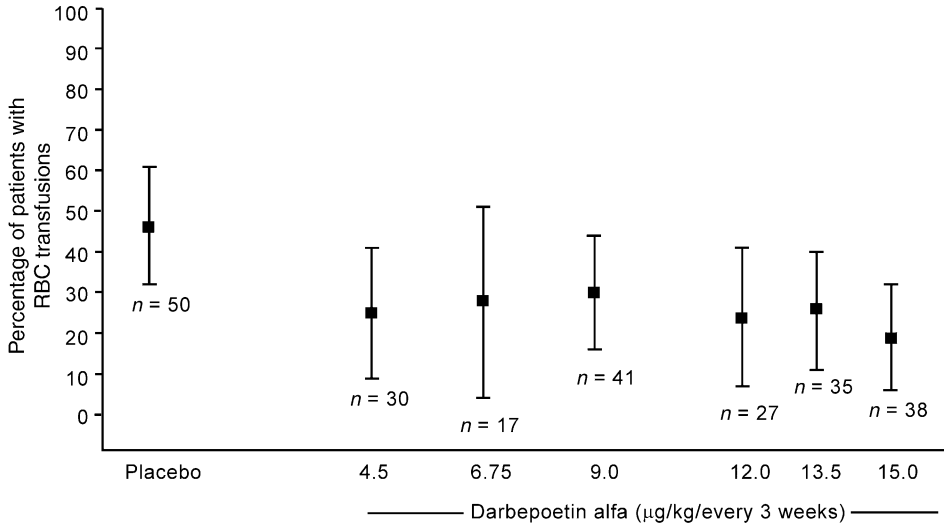

Fig. 7. Red blood cell (RBC) transfusions from week 5 to the end of the treatment phase. Kaplan–Meier proportion shown. Bars represent 95% confidence intervals (CIs).

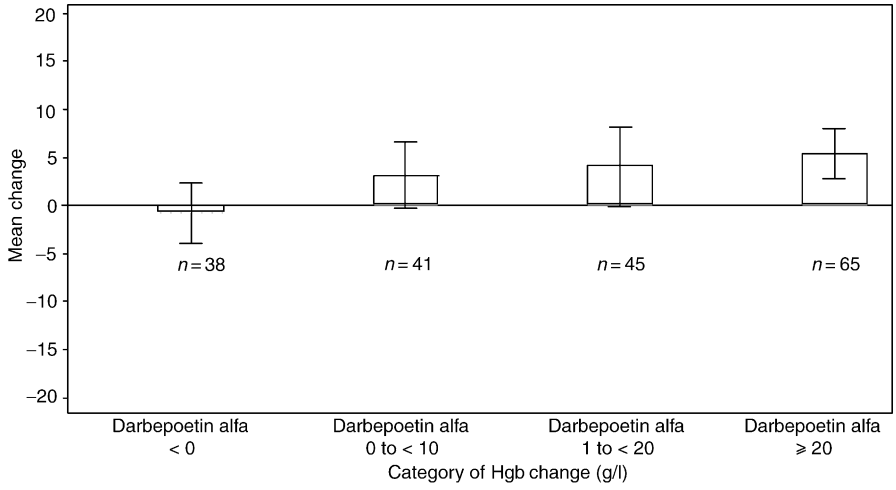

Fig. 8. Change in the health-related quality-of-life FACT-Fatigue score from baseline to the end of the treatment phase by change in haemoglobin. Bars represent 95% confidence intervals (CIs).

The quality-of-life evaluation in this study was designed to assess the feasibility, reliability, validity, sensitivity and timing of quality-of-life surveys in this setting, rather than to evaluate fatigue. Nevertheless, the results demonstrate symptom relief with increasing haemoglobin levels. These findings are consistent with other studies that have shown a correlation between haemoglobin level and quality-of-life measures [3,4].

The safety of Q3W administration of darbepoetin alfa, even at doses as high as 15.0 μg/kg, was generally comparable to that of placebo. The most frequently reported adverse events in both treatment groups were gastrointestinal and constitutional symptoms associated with chemotherapy treatment and cancer. Analysis of serum samples revealed no accumulation of darbepoetin alfa over the course of the study. Unmanageable increases in haemoglobin concentration were not observed. Thrombotic events, seizures and hypertension (of interest based on theoretical concerns from studies of recombinant human erythropoietin in the chronic renal failure population) occurred in comparable proportions of the placebo and darbepoetin alfa patients.

In summary, these results indicate that administration of darbepoetin alfa Q3W is well tolerated and effective in the treatment of anaemic patients receiving chemotherapy. It is of note that despite the relatively high doses used in this study, approximately one-quarter of patients were relatively unresponsive, indicating that research to investigate further improvements in the proportion of patients responding and the timeliness of their response in this setting is warranted. However, we believe that the ability to administer darbepoetin alfa as infrequently as Q3W, as well as the possibility of administering darbepoetin

alfa to coincide with chemotherapy that is administered Q3W, represents an opportunity to simplify the treatment of anaemia and fatigue in cancer patients undergoing chemotherapy.

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Appendix. Additional Members of the Aranesp 980291 study group

Ehtesham Abdi	Bendigo Health Care Group, Bendigo, Victoria, Australia
Joao Baptista-Dapalma	Instituto Costarricense de Investigaciones Clinicas, (ICIC), San Jose, Costa Rica, Central America
Dirk Behringer	Klinikum der Albert-Ludwigs-Universität, Freiburg, Germany
Jonas Bergh	Karolinska Sjukhuset, Stockholm, Sweden
Wolfram Brugger	Eberhard Karls-Universität, Tübingen, Germany
Peter Bryson	Kingston General Hospital, Kingston, Ontario, Canada
A. Hillary Calvert	Newcastle General Hospital, Newcastle upon Tyne, UK
Robert Grimshaw	QEII Health Sciences Centre, Halifax, Nova Scotia, Canada
Peter Harper	Guy's Hospital, London, UK
Rolf Kreienberg	Universitäts-Frauenklinik, Ulm, Germany
Paul Mitchell	Austin & Repatriation Medical Centre, West Heidelberg, VIC, Australia
Bo Nordensköld	Universitetssjukhuset i Linköping, Linköping, Sweden
Jaroslav F. Prchal	St. Mary's Hospital, Montreal, Quebec, Canada
Ian Quirt	Princess Margaret Hospital, Toronto, Ontario, Canada
Bruno Raby	Hopital Laval, Ste. Foy, Quebec, Canada
Jeremy Shapiro	The Alfred Hospital, Prahran, VIC, Australia
Martin Söderberg	Onkologkliniken Centralsjukhuset, Karlstad, Sweden
Silvana Spadafora	Algoma District Medical Group, Sault Ste. Marie, Ontario, Canada
Maureen E. Trudeau	Sunnybrook & Women's College Health Science Centre, Toronto, Ontario, Canada
David Wyld	Prince Charles Hospital, Chermside, QLD, Australia; and Royal Brisbane Hospital, Herston, Australia

References

1. Vogelzang NJ, Breitbart W, Cella D, *et al*. Patient, caregiver, and oncologist perceptions of cancer-related fatigue: results of a tripart assessment survey. *Semin Hematol* 1997, **34**, 4–12.
2. Demetri GD, Kris M, Wade J, *et al*. Quality-of-life benefit in chemotherapy patients treated with epoetin alfa is independent of disease response or tumor type: results from a prospective community oncology study. *J Clin Oncol* 1998, **16**, 3412–3425.
3. Glaspy J, Bukowski R, Steinberg D, *et al*. Impact of therapy with epoetin alfa on clinical outcomes in patients with nonmyeloid malignancies during cancer chemotherapy in community oncology practice. Procrit Study Group. *J Clin Oncol* 1997, **15**, 1218–1234.
4. Gabrilove JL, Cleeland CS, Livingston RB, *et al*. Clinical evaluation of once-weekly dosing of epoetin alfa in chemotherapy patients: improvements in hemoglobin and quality of life are similar to three-times-weekly dosing. *J Clin Oncol* 2001, **19**, 2875–2882.
5. Ludwig H, Fritz E. Anemia in cancer patients. *Semin Oncol* 1998, **25**(Suppl. 7), 2–6.
6. Dammacco F, Castoldi G, Rödjer S. Efficacy of epoetin alfa in the treatment of anaemia of multiple myeloma. *Br J Haematol* 2001, **113**, 172–179.
7. Abels RI. Use of recombinant human erythropoietin in the treatment of anemia in patients who have cancer. *Semin Oncol* 1992, **19**, 29–35.
8. Ludwig H, Barrett-Lee PJ, Gascon P, *et al*. European Cancer Anaemia Survey (ECAS) defines factors surrounding anemia in thousands of adult cancer patients. *Proc Am Soc Clin Oncol*, 2002 (abstr 1546).
9. Egrie JC, Dwyer E, Lykos M, *et al*. Novel erythropoiesis stimulating protein (NESP) has a longer serum half-life and greater in vivo biological activity than recombinant human erythropoietin (rHuEPO). *Blood* 1997, **90**, 56a (abstr 243).
10. Kalbfleisch JD, Prentice RL. *The Statistical Analysis of Failure Time Data*. John Wiley and Sons, Hoboken, 1980 pp. 1–316.
11. Littlewood TJ, Bajetta E, Nortier JWR, *et al*. Effects of epoetin alfa on hematologic parameters and quality of life in cancer patients receiving nonplatinum chemotherapy: results of a randomized, double-blind, placebo-controlled trial. *J Clin Oncol* 2001, **19**, 2865–2874.
12. Cella D, Lai JS, Chang CH, *et al*. Fatigue in cancer patients compared with fatigue in the general United States population. *Cancer* 2002, **94**, 528–538.