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Prevention of anaemia by early intervention with once weekly epoetin alfa during chemotherapy

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ARTICLE INFO

Article history:
Received 28 November 2007
Received in revised form
8 February 2008
Accepted 14 February 2008
Available online 17 March 2008

Keywords:
Anaemia
Blood transfusion
Erythropoietin
Haemoglobin

ABSTRACT

This study compared the effects of early intervention with standard use of epoetin alfa on haemoglobin (Hb) levels and transfusion requirements in cancer patients receiving chemotherapy. Patients with Hb > 10 and ⩽12 g/dL were randomised 1:1 to epoetin alfa (40,000 IU, subcutaneously, once weekly), initiated within 7 d of the start of the first on-study chemotherapy cycle (defined as early intervention) versus epoetin alfa when Hb ⩽ 10 g/dL (defined as standard therapy). Increases in Hb values were significantly higher with early intervention compared to standard therapy from week 6 to 10 ($P \leqslant 0.05$) and approached significance at week 15/16 ($P = 0.0531$). Although the percentage of patients receiving blood transfusions was similar in both groups, the amount of blood transfused was almost twice as high in the standard epoetin alfa group (n.s.). Early intervention with epoetin alfa was well tolerated and overall survival did not differ significantly between groups. Initiation of epoetin alfa at the onset of chemotherapy and Hb < 12 g/dL improves Hb levels significantly versus standard therapy.

1. Introduction

Patients with cancer receiving chemotherapy often develop anaemia, which is associated with poor performance status and decreased quality of life (QOL) and is manifested as fatigue and decreased functional capacity.[1,2] Recombinant erythropoiesis-stimulating agents, such as epoetin alfa, are used for the treatment of chemotherapy-induced anaemia in patients with non-myeloid malignancies.[3] Results of several clinical trials and community-based studies have demonstrated the benefits of administration of epoetin alfa to anaemic patients receiving chemotherapy,[4–11] which include correction of anaemia, reduced transfusion requirement and improvement in QOL. The positive effect of epoetin alfa on QOL is independent of disease response and tumour type[12] and directly related to increases in the haemoglobin (Hb) level.[13]

More recent studies have assessed the effects of an early intervention approach. In this approach, the goal is to begin therapy before Hb levels drop below 10 g/dL and to maintain Hb levels between 10 and 12 g/dL. Evidence-based guidelines for epoetin alfa use established by the American Society of Clinical Oncology and the American Society of Hematology (ASCO/ASH) support this approach, as determined by clinical circumstances.[14] The European Organisation for Research and Treatment of Cancer (EORTC) recommends consideration of early intervention with erythropoietin based on the intensity and expected duration of chemotherapy.[3]

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0959-8049/$ - see front matter
doi:10.1016/j.ejca.2008.02.017

In an open-label, community-based study, early initiation of epoetin alfa improved Hb and QOL relative to baseline in patients with breast cancer.[15] Results of several clinical trials evaluating early intervention in comparison with best supportive care demonstrated that early intervention was superior on endpoints including Hb level, transfusion requirement and QOL.[16–21] However, these studies compared early intervention with control arms that received no epoetin alfa treatment making it difficult to draw conclusions about the benefits of early intervention. At the time of the start of this trial, few studies had compared early intervention directly with standard epoetin alfa therapy. Findings from clinical trials that compared early intervention with delayed intervention have become available.[22–24] These studies have shown that early intervention with epoetin alfa at the start of chemotherapy results in higher Hb levels and lower transfusion rates than delayed intervention. In addition, early intervention appears to maintain QOL in patients with only mild anaemia, potentially avoiding the deterioration of QOL associated with increasingly severe anaemia. A systematic review of the literature also demonstrated that early administration of epoetin alfa, before the onset of anaemia in patients with cancer, resulted in significant reduction in transfusion requirements (significantly fewer patients whose Hb levels fell below 10 g/dL) and significant improvements in QOL.[25] The objective of the current study (Clinical Trials Registry: www.clinicaltrials.gov, NCT00216541) was to compare the effects of early intervention with epoetin alfa with standard use of epoetin alfa on Hb levels and transfusion requirements in patients with cancer receiving chemotherapy.

2. Patients and methods

2.1. Study patients and design

Eligible patients were $\geqslant$18 years of age with a confirmed diagnosis of cancer who were to receive chemotherapy (platinum- or non-platinum containing) in 1-, 2-, 3-, or 4-week schedules for at least 8 or 9 weeks. Patients were included in the study before the start of the first or second chemotherapy cycle if Hb levels >10 g/dL and $\leqslant$12 g/dL during the 14-d period before the start of the first on-study chemotherapy cycle; the Eastern Cooperative Oncology Group (ECOG) performance score was 0, 1 or 2; and the life expectancy was at least 6 months, based on the investigator's clinical judgement. Females were required to be post-menopausal for at least 1 year, sterilised, or, if of childbearing potential, practising an acceptable method of birth control, based on the investigator's clinical judgement.

The original study protocol was amended as follows: after the first 5 patients were enrolled in the study, stricter Hb boundaries were applied (Hb $\leqslant$ 12 g/dL at randomisation and 13 g/dL as the upper limit for administration of epoetin alfa). The inclusion of patients with non-platinum containing chemotherapy and patients starting their second cycle of chemotherapy was also allowed by amendments to the protocol during the study. Finally, the collection of overall survival data was also added by amendment.

Patients with any of the following characteristics were excluded from the study: clinically significant or uncontrolled disease or dysfunction of any body system not attributable to underlying malignancy or chemotherapy, including uncontrolled or severe cardiovascular disease, myocardial infarction within 6 months, uncontrolled hypertension (diastolic blood pressure >95 mm Hg), congestive heart failure, or uncontrolled or unexplained seizures; planned surgery within the first 8–9 weeks of study entry that was judged by the investigator as expected to influence Hb levels; major illness or infection within 1 month of the beginning of the study; highly increased risk of thrombotic or other vascular events, as judged by the investigator; androgen therapy within 2 months of study entry; anaemia due to factors other than cancer or chemotherapy; blood transfusion within 14 d before study entry; participation in any other investigational drug trial or therapy relating to anaemia within 30 d of study entry; current inclusion in any other research project involving unlicensed or experimental medications that would interfere with this study; known hypersensitivity to epoetin alfa or one of its components; pregnancy or currently lactating. Each patient provided written informed consent after the study was fully explained and before any study-related activity was performed.

This was a randomised, open-label, explorative, sequential, multicentre study, with a screening, treatment and end-of-treatment phase (or early withdrawal). Study visits were planned to coincide as much as possible with routine visits for chemotherapy. The protocol and associated amendments were approved by an accredited central independent ethics committee/institutional review board (METOPP, Tilburg, the Netherlands) according to the Dutch Medical Research in Human Subjects Act. The study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation (ICH) and Good Clinical Practice (GCP) guidelines.

The screening visit took place within 14 d before the start of the first on-study chemotherapy cycle, and the following items were collected: informed consent; relevant medical history; chemotherapy, radiotherapy, surgery and transfusion data for the 3 months prior to enrollment; disease symptoms; blood sample for anti-erythropoietin antibody analysis; vital signs; ECOG performance score and concomitant therapy. In addition, the stage of the patient's malignancy was determined, and clinical laboratory tests were carried out.

After screening, patients were randomised 1:1 to receive early intervention (early group) or standard therapy (standard group) according to the adapted minimizations method, after they were determined to fulfil all inclusion criteria by contacting the central randomisation centre. The starting dose of epoetin alfa (Eprex®; Ortho Biotech/Janssen-Cilag, High Wycombe, United Kingdom; [also marketed in the United States as Procrit®; Ortho Biotech Products, L.P., Bridgewater, NJ]) was 40,000 IU, s.c., once weekly (QW). Patients in the early group received their first dose within 7 d after day 1 of the first on-study chemotherapy cycle. Patients in the standard group received their first dose as soon as their Hb was $\leqslant$10 g/dL. All patients received epoetin alfa until 1, 2, 3, or 4 weeks after the start of their last chemotherapy cycle (for patients receiving chemotherapy every 1, 2, 3, or 4 weeks, respectively), up to a maximum of 24 weeks. A gradual increase in Hb of up to 2 g/dL per month during treatment was recommended, epoetin alfa was not to be administered at Hb levels above 13 g/dL, and Hb levels were not to rise above 14 g/dL; therefore, Hb was monitored at least every 2 weeks.

Dose adjustments were made according to the following criteria: when Hb > 13 g/dL, epoetin alfa was discontinued temporarily and resumed at 40,000 IU QW when Hb < 12 g/dL; epoetin alfa was never administered if Hb > 13 g/dL. If Hb did not increase >1 g/dL after the first 4 weeks of treatment or within any 4-week period thereafter, the dose was modified by doubling it to 80,000 IU QW, as long as Hb was not >12 g/dL.

Patients were to receive an oral iron supplementation three times daily. Investigators could instruct patients to discontinue iron supplementation temporarily if they were already experiencing gastrointestinal problems related to chemotherapy or other concomitant medication and the iron supplementation was expected to worsen these problems significantly, or if they were unable to receive iron supplementation because of nausea or vomiting.

In both groups, transfusions were administered as necessary, based on clinical judgement. Efforts were made not to transfuse patients with Hb > 9.7 g/dL. Deficiencies of folic acid and vitamin B12 were managed according to common medical practice.

At study visits 2–8, Hb, haematocrit, transfusion data, chemotherapy data, adverse events and concomitant therapy were recorded before the start of the next cycle of chemotherapy. At visits 3, 5, and 7, ferritin, transferrin saturation, folic acid and vitamin B12 levels were monitored, vital signs were recorded, and ECOG performance was scored by the investigator. Within 7 d of the last dose of epoetin alfa, the end-of-study visit took place, and the following items were collected: blood sample for anti-erythropoietin antibody analysis; Hb, haematocrit, ferritin, transferrin saturation, folic acid and vitamin B12 levels; vital signs; ECOG performance score; chemotherapy, radiotherapy, surgery, and transfusion data; adverse events; and concomitant therapy.

2.2. *Evaluation of efficacy and safety*

The primary efficacy variables were the mean change in Hb after weeks 3/4, 8/9, and 12, and at the end of treatment, and the proportion of patients who had an allogeneic blood transfusion during the study period. Safety evaluations included the assessment of survival, incidence and severity of adverse events, clinical laboratory tests and vital signs. Survival data were collected after the last patient in the study had completed the last visit. Adverse events were reported starting from the first trial-related procedure until the last visit, and all were followed until resolution or until a stable clinical endpoint was reached.

Hb levels were analysed to account for the difference in study duration across patients, particularly with regard to the study end visit. With the aim to interpret the results of the end visits in the study weeks when they were actually determined, the data from the end visits were analysed in the study week in which the end visit actually took place. In these analyses, only those end visits taking place after week 15/16 were considered 'end visits' (and are represented graphically as such), as they took place 3 or 4 weeks after study week 15/16, at a minimum. For all patients, an 'endpoint' was also analysed, representing the last measurement for that patient on study (which could have taken place during different study weeks).

2.3. *Anti-erythropoietin antibody testing*

Blood samples (10 mL) were collected from patients before the initiation of epoetin alfa therapy and at the end-of-study visit after the last administration of epoetin alfa during study. Blood of these samples was allowed to clot at room temperature for approximately 15–30 min, placed on ice, and centrifuged at about 1000*g* for 10 min. Serum was collected and stored at −20 °C or on dry ice and shipped to a central laboratory, where it was analysed for anti-erythropoietin antibodies and circulating erythropoietin concentration.

2.4. *Statistical analyses*

A preliminary calculation of the sample size that would enable a comparison of early and late intervention was performed, with the differences in mean Hb levels of both groups estimated at 1.5 (with a common standard deviation of 2.0). With an α of 0.05 and a power of 80%, 33 patients per group were needed to complete the study. Assuming an early withdrawal rate of 15%, approximately 40 patients would be needed per group. However, data from the planned interim analysis indicated a dropout rate (percentage who did not reach a 12-week period on study) of at least 40%, caused mainly by a pre-mature stop of chemotherapy. Therefore, 110 patients were enrolled.

Efficacy was assessed for the intent-to-treat population (ITT), which included all randomised patients with at least one post-baseline efficacy measurement. For the analysis of Hb values per day, Hb values for each patient were carried forward until a new value was available. The number and percentage of patients who received blood transfusions during the treatment phase were summarised as a frequency distribution for each group and tested with the Fisher exact test. Within-group differences were evaluated with the Wilcoxon signed rank test, and between-group differences were evaluated with the Wilcoxon two-sample test.

The safety population was defined as all randomised patients for whom assessments of safety parameters were available. The Medical Dictionary for Regulatory Activities (MedDRA) was used to code all reported adverse events, and adverse events were categorised by body system and preferred term. Between-group differences were tested using the Fisher exact test. Mean survival time, standard deviation and the 95% confidence interval (CI) were calculated for each group. The number of patients deceased or censored was summarised as a frequency distribution for each group. Survival curves were analysed using the Kaplan–Meier technique, and between-group differences were assessed with the Log-rank test.

Unless otherwise indicated, the term 'significant' refers to 'statistically significant' throughout this paper.

3. Results

This study was initiated in September 2003 and completed in September 2006. Of the 110 patients enrolled, 108 were evaluable. A study flowchart of patient disposition is included in Fig. 1. For 2 patients, no post-baseline measurements were obtained because they discontinued the study before any data

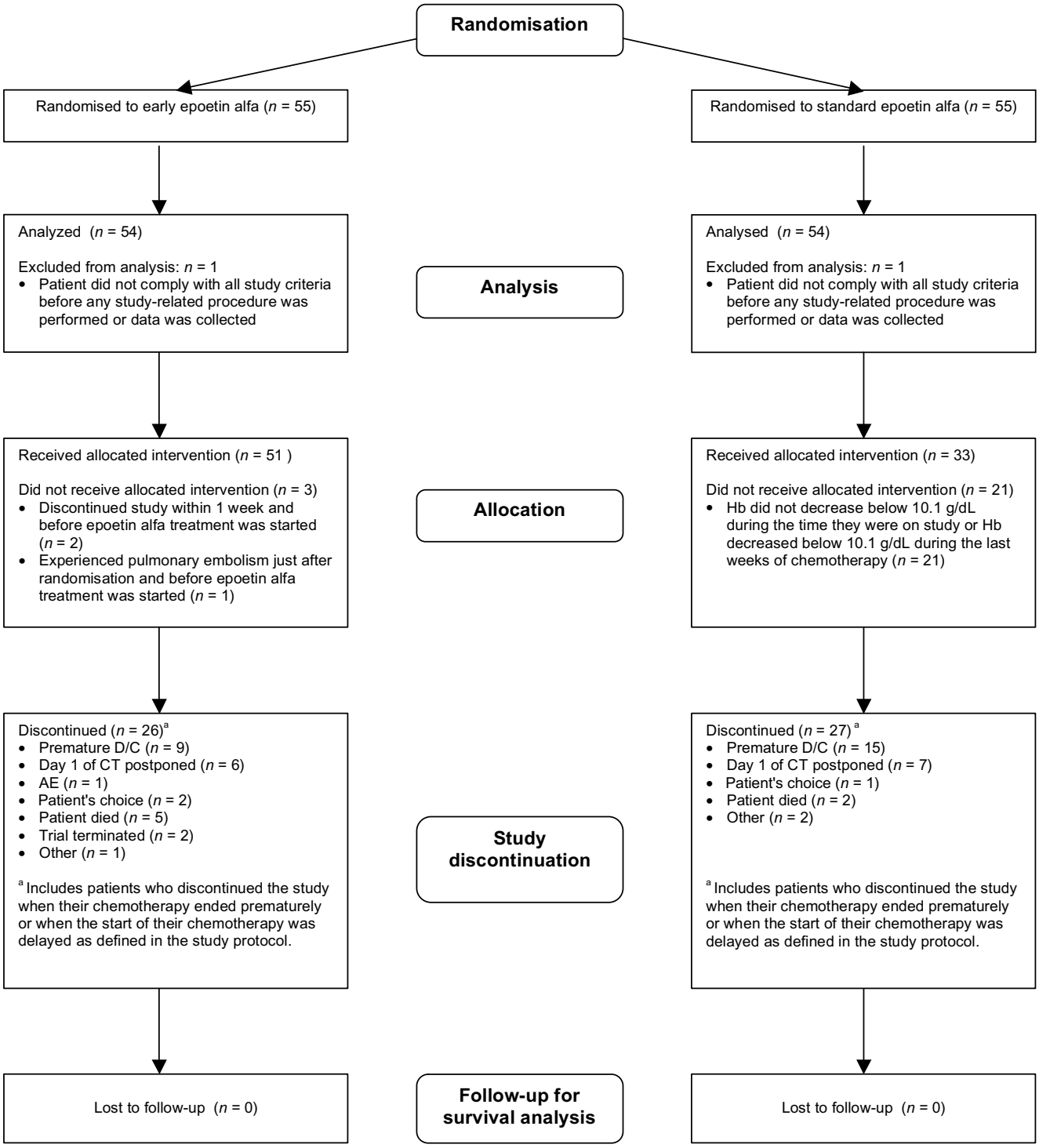


Fig. 1 – Study flowchart. Hb, Haemoglobin; D/C, discontinuation; CT, chemotherapy; AE, adverse events.

were collected. Almost half (49%) of the patients discontinued the study pre-maturely; the most common reason was premature discontinuation of scheduled chemotherapy (early group, $n = 9$; standard group, $n = 15$). Other reasons included day 1 of chemotherapy postponed >9 d (early group, $n = 6$; standard group, $n = 7$), adverse event (early group, $n = 1$ [diarrhoea, dry mouth, rhinorrhaea]), patient's choice (early group, $n = 2$; standard group, $n = 1$), death (early group, $n = 5$; standard group, $n = 2$) and other (early group, $n = 3$; standard group, $n = 2$). Epoetin alfa was administered to 51 (94%) patients in the early group and 33 (61%) in the standard group. Ten patients in the early group and 4 in the standard group had their dose doubled due to an Hb response of <1 g/dL within 4 weeks. The mean dose of epoetin alfa did not differ

significantly between groups. Among patients who received epoetin alfa during the study, the percentage of patients using iron did not differ significantly between groups (early group, 92%; standard group, 91%).

Table 1 – Baseline demographics and clinical characteristics

Characteristic	Early EPO (n = 54)	Standard EPO (n = 54)
Sex, n (%)		
Male	26 (48.1)	27 (50.0)
Female	28 (51.9)	27 (50.0)
Mean age, years (SD)	60.0 (10.8)	61.7 (12.3)
ECOG performance score, n (%)		
0	20 (37.0)	19 (35.2)
1	29 (53.7)	29 (53.7)
2	5 (9.3)	6 (11.1)
Mean ECOG performance score (SD)	0.7 (0.6)	0.8 (0.6)
Primary site of malignancy, n (%)		
NSCLC	16 (29.6)	22 (40.7)
SCLC	14 (25.9)	6 (11.1)
Ovary	5 (9.3)	8 (14.8)
Colon	2 (3.7)	7 (13.0)
Breast	5 (9.3)	1 (1.9)
Bladder	2 (3.7)	3 (5.6)
Other	10 (18.5)	7 (13.0)
Metastatic disease, n (%)	35 (65)	33 (61)
Hb, g/dL, mean (SD)	11.2 (0.80)	11.2 (0.70)
Chemotherapy, n (%)	54 (100)	54 (100)
Radiotherapy, n (%)	3 (5.6)	5 (9.3)

EPO, epoetin alfa; SD, standard deviation; ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small-cell lung cancer; SCLC, small-cell lung cancer; Hb, haemoglobin.

3.1. *Demographics and baseline clinical characteristics*

The demographics and baseline clinical characteristics of the ITT efficacy population are listed in Table 1. The treatment groups were well balanced at baseline. The mean baseline Hb level was 11.2 g/dL, and most patients had an ECOG performance score of 0 or 1. The most common type of malignancy was non-small-cell lung cancer (NSCLC; 35%). All patients received chemotherapy during the study, less than 10% received radiotherapy (both for palliative purposes or as part of the anti-cancer therapy), and surgery was performed only for two subjects in the early group (lower leg amputation, embolectomy). The percentage of patients with metastatic disease was comparable in both groups (65% in the early group versus 61% in the standard group).

3.2. *Haemoglobin responses*

Mean changes in Hb levels over time in each group are shown in Fig. 2 when analysed as Hb values per day. Hb values increased and stabilised in the early intervention group while Hb values decreased in the standard group. When the Hb values are analysed at the different study visits, mean Hb values were significantly higher in the early group compared with the standard group at weeks 6, 8/9, 10 and 15/16 ($P < 0.05$; Fig. 3A). The increases in Hb in the early group were significant relative to baseline at weeks 6, 10, 15/16, and the end visit ($P < 0.05$), and were significantly higher compared to those in the standard group at weeks 6, 8/9 and 10 ($P < 0.05$) and approached significance at week 15/16 ($P = 0.0531$; Fig. 3B).

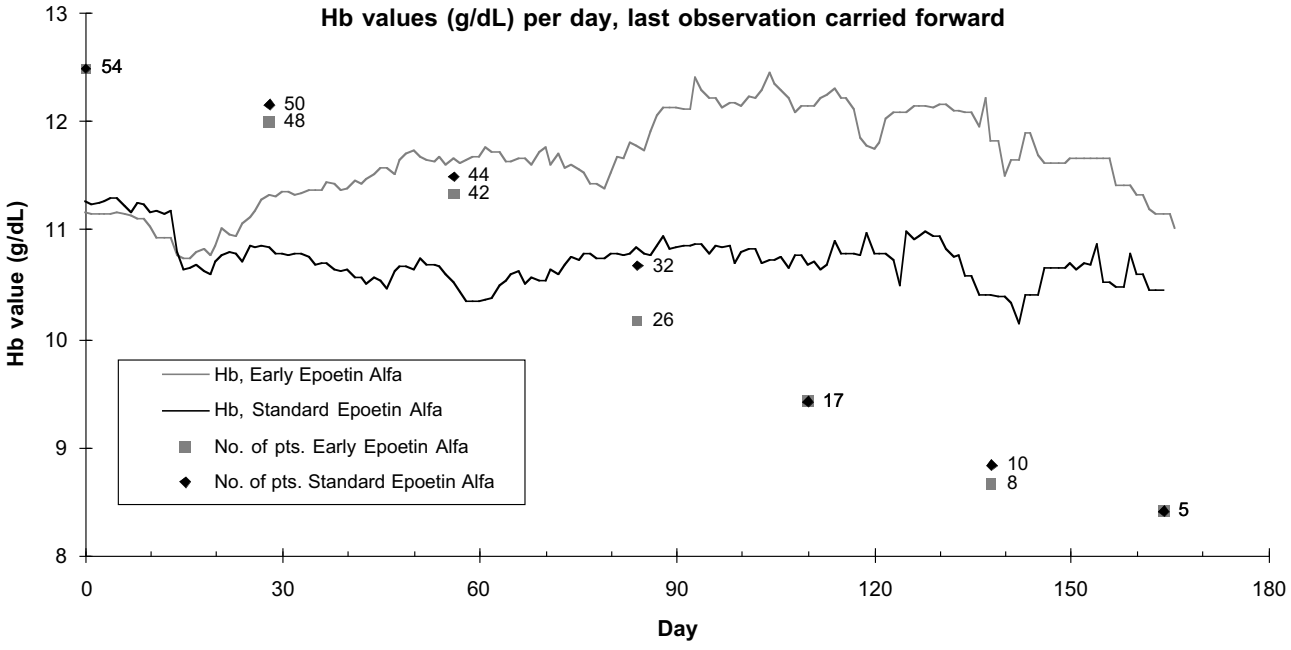
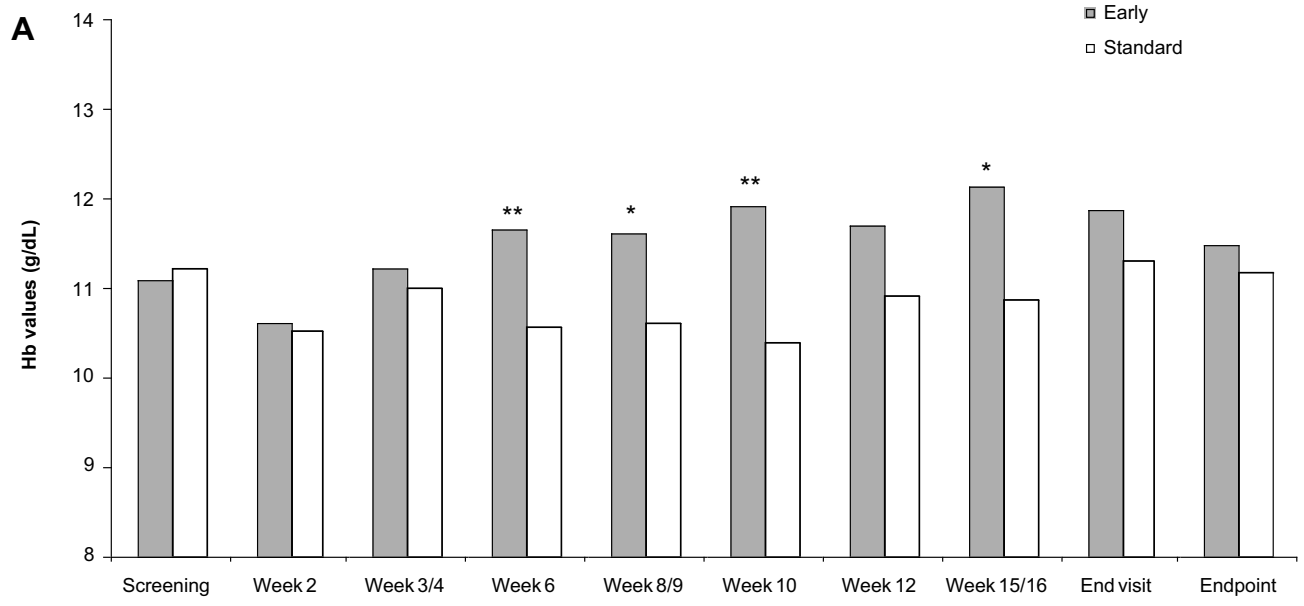
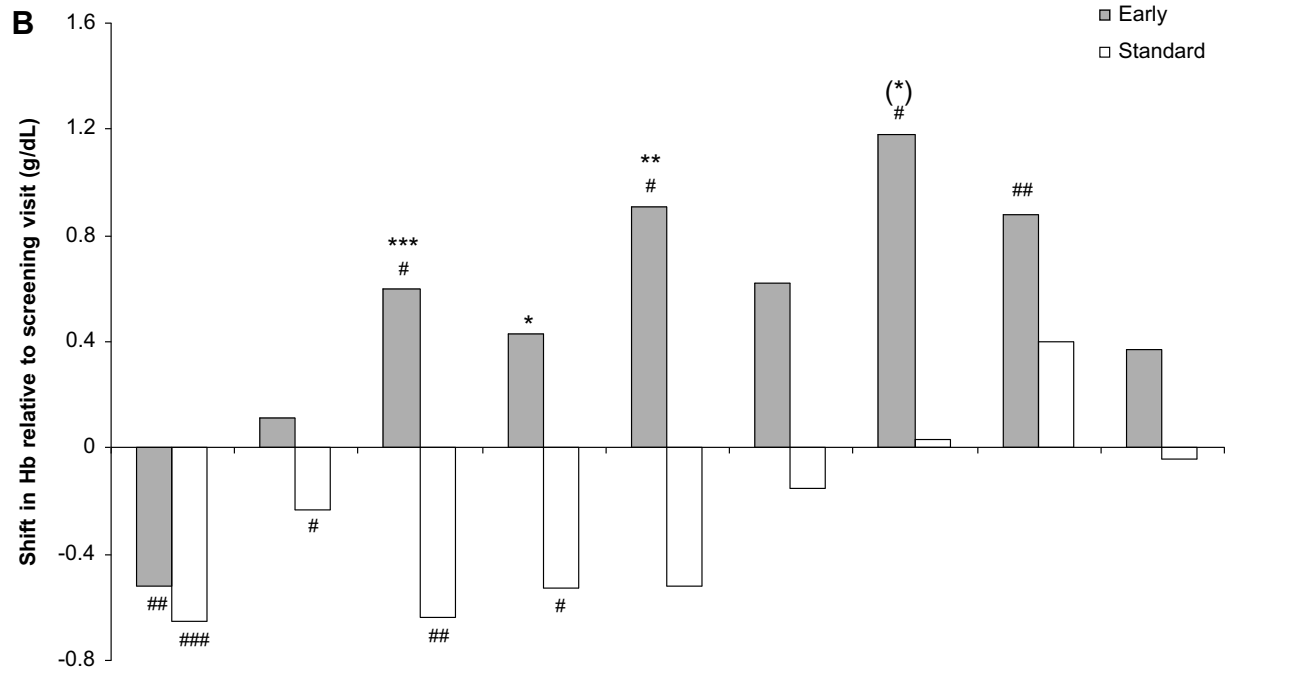


Fig. 2 – Mean daily haemoglobin (Hb) levels for patients treated with early or standard epoetin alfa. Mean Hb values based on fewer than 5 patients in each treatment group are not presented.



SD(±)	Screening	Week 2	Week 3/4	Week 6	Week 8/9	Week 10	Week 12	Week 15/16	End visit	Endpoint
Early	0.75	1.39	1.35	1.74	2.07	1.70	2.05	1.16	1.20	1.84
Standard	0.70	0.98	1.16	1.13	1.33	1.34	1.61	1.51	1.65	1.37



SD(±)	Week 2	Week 3/4	Week 6	Week 8/9	Week 10	Week 12	Week 15/16	End visit	Endpoint
Early	1.06	1.34	1.74	2.07	1.81	1.92	1.43	1.04	1.76
Standard	0.92	1.14	1.34	1.48	1.46	1.68	1.39	1.64	1.56

Fig. 3 – (A) Mean haemoglobin levels during the study. (B) Shifts in haemoglobin levels during the study. $^{*}P < 0.05$ for between-group difference; $^{**}P < 0.01$ for between-group difference; $^{***}P < 0.001$ for between-group difference; $^{\#}P < 0.05$ versus baseline; $^{\#\#}P < 0.01$ versus baseline; $^{\#\#\#}P < 0.001$ versus baseline; $(^{*})P = 0.0531$ for between-group difference. SD, standard deviation.

3.3. *Transfusion requirements*

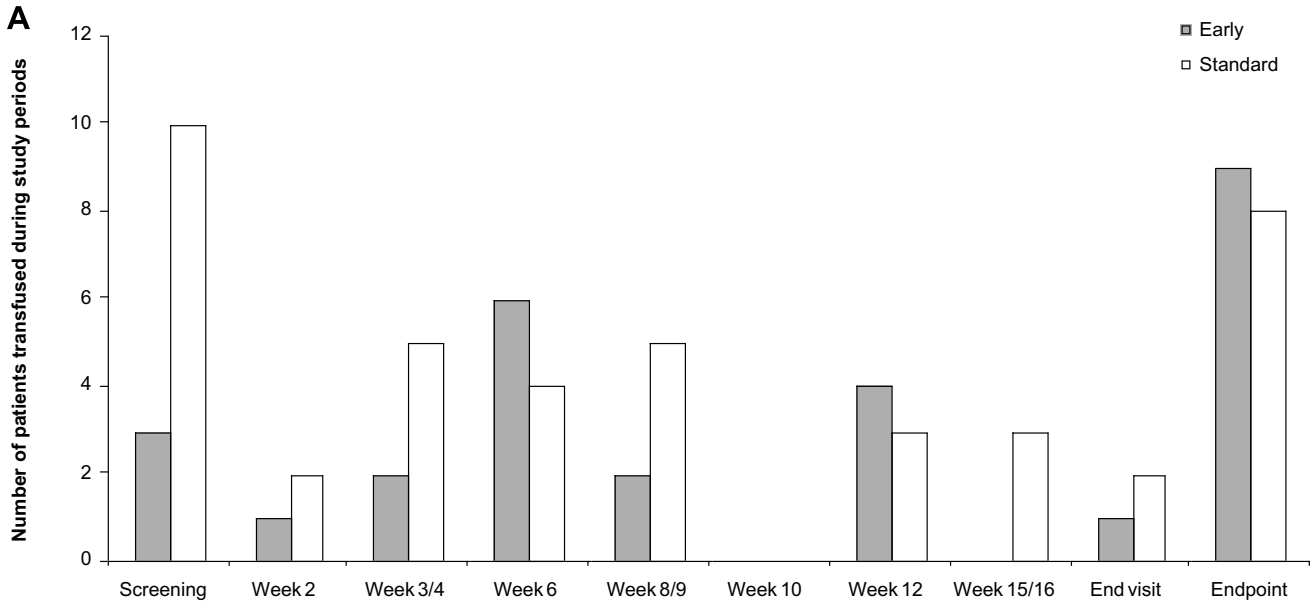
The number of patients who required a transfusion during the treatment period did not differ between groups; 15 patients (28%) in both study groups were transfused during the complete study period (Table 2). The mean volume transfused and the mean number of transfusions were greater in the standard group compared with the early group but these differences were not significant. The number of patients transfused and the mean volume transfused are indicated per

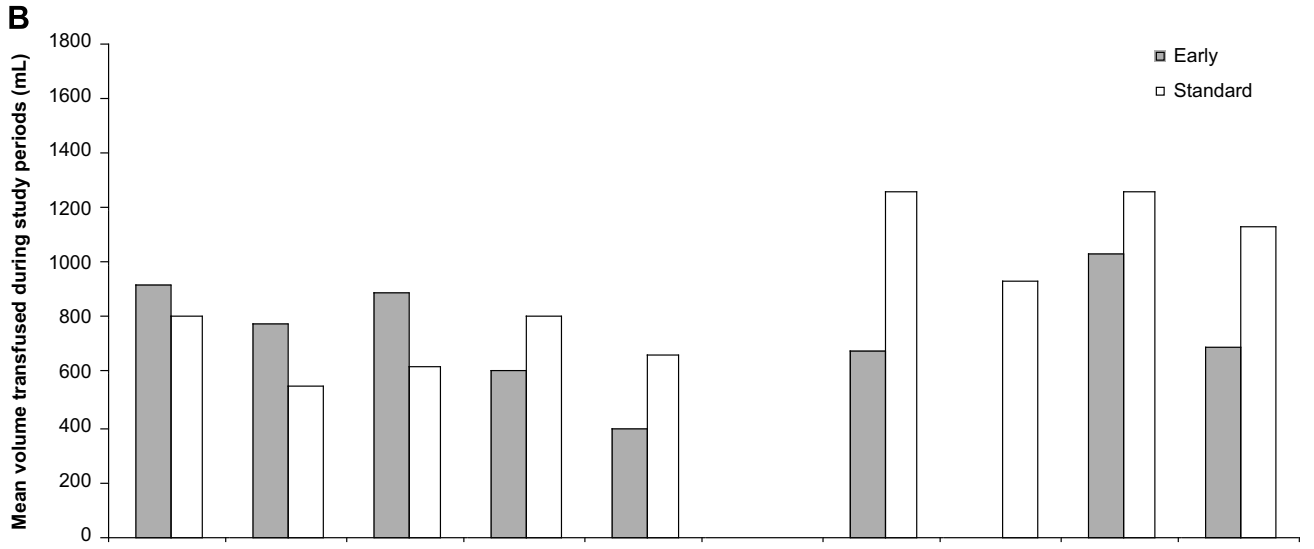
Table 2 – Patients requiring transfusion during the complete study period

	Early EPO (n = 54)	Standard EPO (n = 54)	P-value
Patients transfused, n (%)	15 (28)	15 (28)	1.0000
Volume transfused (mL), mean (SD)	723 (335)	1330 (1166)	0.1480
Number of transfusions per patient, mean (SD)	1.4 (0.5)	2.2 (1.9)	0.3073

EPO, epoetin alfa; SD, standard deviation.

study visit in Fig. 4A and B, respectively. Although the absolute number of patients transfused during the complete study period is similar for both study groups, patients were more frequently transfused in the standard group compared to the early group. The mean Hb values before the first transfusion were not statistically significantly different between both





SD(±)	Screening (n=3/10)	Week 2 (n=1/2)	Week 3/4 (n=2/5)	Week 6 (n=6/4)	Week 8/9 (n=2/5)	Week 10 (n=0/0)	Week 12 (n=4/3)	Week 15/16 (n=0/3)	End visit (n=1/2)	Endpoint (n=9/8)
Early	161.7	–	205.1	285.8	148.5	–	375.0	–	–	311.0
Standard	320.4	70.7	133.7	485.9	212.8	–	1322.1	271.4	685.9	822.1

Fig. 4 – (A) Transfusions during study periods. (B) Mean volume transfused during study periods. In Fig. 4B, the number of patients transfused during each study period is shown in parentheses. SD, standard deviation.

Table 3 – Incidence of most common adverse events

Adverse event, *n* (%)	Early EPO (*n* = 54)	Standard EPO (*n* = 54)
Any adverse event	52 (96.3)	54 (100)
Nausea	18 (33.3)	24 (44.4)
Fatigue	13 (24.1)	24 (44.4)
Anaemia	12 (22.2)	15 (27.8)
Vomiting	10 (18.5)	13 (24.1)
Constipation	8 (14.8)	12 (22.2)
Diarrhoea	5 (9.3)	12 (22.2)
Pyrexia	12 (22.2)	5 (9.3)
Neuropathy	8 (14.8)	8 (14.8)
Dyspnoea	5 (9.3)	9 (16.7)
Alopecia	6 (11.1)	6 (11.1)
Leucopenia	7 (13.0)	5 (9.3)
Thrombocytopenia	8 (14.8)	4 (7.4)
Dizziness	3 (5.6)	7 (13.0)
Abdominal pain upper	2 (3.7)	6 (11.1)

EPO, epoetin alfa.
Note: Adverse events reported in at least 10% of patients in either treatment group.

study groups (early group: 4.99 ± 0.46 mmol/L; standard group: 5.27 ± 0.47 mmol/L; $p = 0.1001$).

3.4. *Safety evaluation*

Common adverse events did not differ significantly in incidence between groups (Table 3), and most were mild or moderate in intensity. Treatment-related adverse events were rare, and included fatigue (early group, $n = 0$; standard group, $n = 1$), bone pain (early group, $n = 1$; standard group, $n = 0$) and thrombophlebitis (early group, $n = 1$; standard group, $n = 0$); all were classified as possibly related to treatment.

Efforts were made to identify adverse events which may have been caused by a thrombovascular event, although evidence for such a relation was not found for all cases. The possible thrombovascular events reported in this study can be subdivided into four classes: (1) unequivocal thromboembolic events (thrombosis, pulmonary embolism); (2) arterial vascular diseases (myocardial infarction, cerebral infarction); (3) possible arterial vascular diseases (cardiac arrest, cardiac failure, circulatory collapse, shock); and (4) superficial venous phenomena ([thrombo]phlebitis, vasculitis, angiopathy, peripheral embolism).

Unequivocal thrombovascular events that occurred during the study were pulmonary embolism (early group, $n = 4$ versus standard group, $n = 1$) and thrombosis (early group, $n = 0$ versus standard group $n = 1$). Arterial vascular disease occurred as 1 versus 1 case, possible arterial vascular disease as 5 versus 4 cases and superficial venous phenomena as 6 versus 2 cases in the early versus standard groups, respectively. Two patients each experienced two possible thrombovascular events (one patient in the early group experienced both pulmonary embolism and shock and one patient in the standard group experienced both thrombosis and shock). One patient in the early group with pulmonary embolism did not use epoetin alfa during the study. In the standard group, for one case of cardiac failure, one case of myocardial infarction, one case of shock, one case of thrombosis and two cases

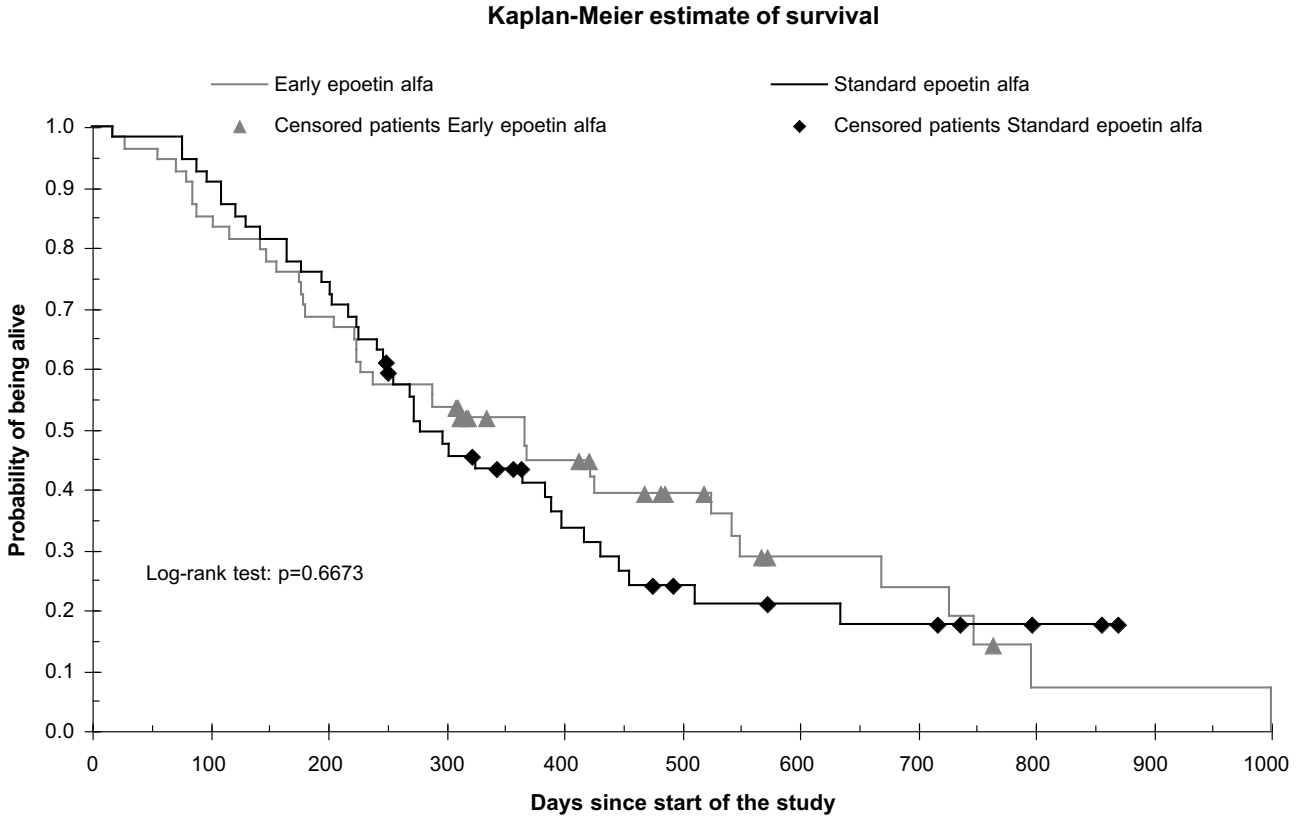


Fig. 5 – Kaplan–Meier estimate of overall survival (safety population).

of phlebitis, patients did not use epoetin alfa during the study.

Serious adverse events were experienced by 38% of patients (early group, $n = 21$; standard group, $n = 20$). The most common were pyrexia, pancytopenia, leucopoenia and anaemia. Serious adverse events prompted dose adjustments in 3 patients in the standard group. Most were classified as having no relationship to treatment; 5 were classified as having a doubtful relationship to treatment.

A slightly greater percentage of patients in the standard group versus the early group developed a clinically significant abnormality, as judged by the investigators, in ferritin (4% versus 0%, respectively) and in transferrin/iron saturation (6% versus 2%, respectively). No clinically significant folic acid or vitamin B12 abnormalities were noted, as judged by the investigators, in either group.

No anti-erythropoietin antibodies were detected in samples from the treatment groups either before or after treatment with epoetin alfa.

3.5. *Survival*

A total of 13 patients died during the study (early group, $n = 8$; standard group, $n = 5$). None of the deaths were considered by the investigator to be related to study medication. During both treatment and follow-up, 39 patients died in the early group, and 40 patients died in the standard group. The median survival time was 367 d (95% CI: 225–542 d) in the early group and 278 d (95% CI: 247–389 d) in the standard group with a median follow-up time (excluding patients who died during the study) of 235 d (95% CI: 215.8–334.5 d) in the early group and 196 d (95% CI: 188–294 d) in the standard group. Kaplan–Meier analysis is shown in Fig. 5; there was no significant difference in survival between groups (Log-rank test, $P = 0.6673$).

4. Discussion

The results of this study indicate that early administration of epoetin alfa significantly improves Hb levels versus standard therapy in patients with cancer receiving chemotherapy. Although both dosing schedules have been shown in the literature to reduce transfusion requirements versus best supportive care, they performed similarly in this head-to-head comparison. The percentage of patients transfused during this study was similar in both groups; however, the total amount transfused and the number of transfusions was greater in the standard group versus the early group, although the difference was not significant and the conclusion is based on a relatively small number of patients. In a similar study, early administration of epoetin alfa (upon initiation of chemotherapy) effectively maintained Hb levels throughout the study compared with a decrease from baseline in Hb level with standard therapy (no epoetin alfa unless Hb $\leqslant$ 10 g/dL) (12.9 g/dL versus 11.6 g/dL mean final values, respectively).[24] The percentage of patients transfused during the study was lower in the early group compared with that in the standard group (11.3% versus 18.1%, respectively); the difference, however, was not statistically significant. Early administration of epoetin alfa was well tolerated in the current trial. Most of the common adverse events and serious adverse events observed were well-documented sequelae of chemotherapy. The number of patients with (possible) thrombovascular events was slightly higher with early epoetin alfa administration. However, no difference in overall survival was observed between the early and standard administration schedules. A recent meta-analysis of 57 trials also suggested no association between epoetin alfa administration and survival.[26]

Recently, the United States Food and Drug Administration revised the labelling for erythropoiesis-stimulating agents to include a boxed warning regarding an increased risk of death and serious cardiovascular events when these agents are administered to achieve Hb levels >12 g/dL or when patients with cancer-related anaemia not receiving chemotherapy are treated with erythropoiesis-stimulating agents. In addition, the boxed warning recommends use of the lowest dose necessary to maintain Hb levels that avoid transfusion. In this trial, Hb levels were monitored routinely, and epoetin alfa was never to be administered if Hb > 13 g/dL, in line with the product labelling at the time this study was conducted. The dosage of 40,000 IU QW was based on 2002 ASCO/ASH guidelines and clinical data indicating correction of anaemia, reduced transfusion requirements, and improved QOL in patients with cancer receiving chemotherapy.[7,27] Doubling of the dosage in patients with an Hb increase <1 g/dL after the first 4 weeks was based on ASCO/ASH guidelines as well.[27]

QOL was not measured in the current study, so it is not known whether one administration schedule provided a greater overall QOL benefit. Given the QOL benefits observed in studies that used either early intervention or standard therapy, it is likely that both approaches would have improved QOL relative to baseline. However, given the established relationship between the effect of epoetin alfa therapy on QOL and Hb level,[13] it is possible that the early intervention group may have had improved QOL versus standard therapy. A recent comparison of the effects of early (Hb 10–12 g/dL) and late (Hb < 9 g/dL) intervention on QOL in patients with haematologic malignancies showed that the early intervention group achieved significantly higher Hb levels and QOL scores than the late intervention group.[23] In addition, an open-label study in chemotherapy-naïve patients with NSCLC demonstrated favourable trends for Hb levels, transfusion use, and QOL with early intervention over standard use with no detrimental effects.[24] In this study, however, no statistically or clinically significant differences between the two intervention groups on QOL measurements were found. However, the study did not reach the planned number of patients, which reduced the statistical power and may have contributed to the lack of significance for QOL. A recent study of darbepoetin alfa in chemotherapy-induced anaemia confirmed the direct and positive relationship between Hb levels and QOL.[28] Patients treated with darbepoetin alfa who experienced a Hb change of >2 g/dL from baseline with either early (within 4 d of randomisation) or delayed (Hb < 10 g/dL) administration schedule had clinically meaningful ($\geqslant$3-point change) improvements in fatigue QOL score. However, improvement in QOL score was not statistically significant between the two intervention groups.

Since the publication of the 2002 ASCO/ASH guidelines,[27] a number of studies have shown potential clinical benefit of

starting epoetin alfa therapy at Hb levels >10 g/dL in terms of lower transfusion requirements and improved QOL outcomes when compared with standard intervention (when Hb levels reach ⩽10 g/dL).[23,24,28] Although the potential risk for thrombovascular events appears slightly higher with early epoetin alfa administration compared with standard use, the findings of the current trial are comparable with the results reported in the published literature. Similar to the 2002 ASCO/ASH guidelines, the 2007 guidelines recommend that the decision to use epoetin alfa or darbepoetin alfa for patients with declining Hb levels but less severe anaemia (Hb < 12 g/dL but not near 10 g/dL) (i.e. early intervention) be made based on clinical circumstances (e.g. elderly patients with limited cardiopulmonary reserve).[14]

In conclusion, initiation of epoetin alfa at the onset of chemotherapy in patients with Hb < 12 g/dL significantly improves and maintains Hb levels but the percentages of patients transfused was similar, versus treatment with epoetin alfa when Hb levels decrease to <10 g/dL. Epoetin alfa was well tolerated, and no difference was shown between the survival curves of the early versus the standard group.

Conflict of interest statement

Dr. Schouwink, Dr. Codrington, Dr. Sleeboom and Dr. Kerkhofs received investigator fees. Dr. Wormhoudt is an employee of Janssen-Cilag B.V., the Netherlands, and owns stock in Johnson and Johnson.

Acknowledgements

This study was financially supported by Ortho Biotech, a division of Janssen-Cilag B.V., the Netherlands. Ortho Biotech was involved in the protocol development, study design, collection, analysis and interpretation of the data, writing of the manuscript, and in the decision to submit the manuscript.

The following investigators contributed to and enrolled patients into this study: Baas A.A.F., den Boer M.O., Brahim J.J., Braun J.J., Codrington H.E., Coenen J.L.L.M., Colder C.D., Deprés-Brummer P., Dullemond A.C., de Graaf J.C., van der Heul C., Honkoop A., Kerkhofs L.G.M., Kok T.C., Koolen M.G.J., Lammers E., van de Moosdijk C.N.F., Nortier J.W.R., Pinson P., Portielje J.E.A., Ruit J., Schouwink J.H., Simons J.P.F.H.A., Sleeboom H.P., Slingerland R., Smals A.E.M., Smeets M.E.P., Smit J.M., Valster F.F.A., van der Velden P.C., van Velzen E., Wielenga J.J.

The authors acknowledge Roseanne Degnan (Scientific Connexions, Newtown, PA), for providing medical writing and editorial support, and Marieke Buitenhuis and Marjolein Lahaye for the data management and statistical analysis, respectively.

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