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Effects of early intervention with epoetin alfa on transfusion requirement, hemoglobin level and survival during platinum-based chemotherapy: Results of a multicenter randomised controlled trial

J.H. Savonije [a], C.J. van Groeningen [a], A. van Bochove [b], A.H. Honkoop [c], C.L. van Felius [d], L.W. Wormhoudt [e], G. Giaccone [a,*]

[a] *VU Medisch Centrum, De Boelelaan 1117, 1081 HV Amsterdam, The Netherlands*
[b] *De Heel Zaans Medisch Centrum, Zaandam, The Netherlands*
[c] *Isala Klinieken, Zwolle, The Netherlands*
[d] *Twenteborg Ziekenhuis, Almelo, The Netherlands*
[e] *Ortho Biotech, a division of Janssen-Cilag B.V., Tilburg, The Netherlands*

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Abstract

This work was conducted to evaluate the effect of early intervention with epoetin alfa (EPO) on transfusion requirements, hemoglobin level (Hb), quality of life (QOL) and to explore a possible relationship between the use of EPO and survival, in patients with solid tumors receiving platinum-based chemotherapy. Three hundred and sixteen patients with Hb $\leqslant$ 12.1 g/dL were randomised 2:1 to EPO 10 000 IU thrice weekly subcutaneously (n = 211) or best supportive care (BSC) (n = 105). The primary end point was proportion of patients transfused while secondary end points were changes in Hb and QOL. The protocol was amended before the first patient was recruited to also prospectively collect survival data. EPO therapy significantly decreased transfusion requirements ($P < 0.001$) and increased Hb ($P < 0.005$). EPO-treated patients had significantly improved QOL compared with BSC patients ($P < 0.05$). Kaplan–Meier estimates showed no differences in 12-month survival ($P = 0.39$), despite a significantly greater number of patients with metastatic disease in the EPO group (78% *vs.* 61%, $P = 0.001$). EPO was well tolerated. This study has shown that early intervention with EPO can result in a significant reduction of transfusion requirements and increases in Hb and QOL in patients with mild anemia during platinum-based chemotherapy.

Keywords: Platinum-based chemotherapy; Anemia; Epoetin alfa

1. Introduction

Anemia is a frequent complication of chemotherapy, occurring in approximately 20–60% of cancer patients during treatment [1,2]. Chemotherapy-associated anemia may cause symptoms such as fatigue, exhaustion, dizziness, sleeping disturbances, decreased appetite, headaches and heart failure to result in decreased functional capacity and impaired quality of life (QOL). Red blood cell transfusion has long been the only treatment modality for anemia during chemotherapy. Concerns about the safety of donor blood, related to the possible transmission of infectious diseases (cytomegalovirus, hepatitis, and HIV), allergic reactions and hypervolemia (which can lead to heart failure) have led to a tendency to treat only severe anemia. With the introduction of epoetin alfa (EPO) therapy in the 1990s an alternative therapy for chemotherapy-associated anemia became available. There is evidence that EPO is effective in

* Corresponding author. Tel.: +31 20 4444321; fax: +31 20 4444079.
E-mail address: g.giaccone@vumc.nl (G. Giaccone).

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decreasing transfusion requirements and increasing Hb, functional capacity and QOL during chemotherapy [3,4]. Most trials have investigated the effect of EPO on moderate to severe anemia and current clinical practice guidelines recommend the use of EPO from Hb < 10 g/dL [5]. However, when data from two large community-based studies were pooled to evaluate the correlation between Hb change and QOL, a strong non-linear relationship between Hb and QOL was demonstrated. The greatest gain in QOL occurred at an increase of Hb from 11 to 13 g/dL [6]. A recently published large randomised trial as well as several reports also support early intervention with EPO [7–10]. In the current study, we have tested the hypothesis that EPO therapy would reduce transfusion requirement and increase QOL in patients with mild to moderate anemia (Hb $\leqslant$ 12.1 g/dL). Shortly after completing the protocol, a possibly positive effect of EPO on patient survival was reported [11]. For this reason the study protocol was amended prior to patient recruitment to permit prospective analysis of survival.

2. Patients and methods

2.1. Study patients and design

This was a prospective, open-label, randomised, multicenter study. Patients were recruited from 15 hospital clinics in the Netherlands. The design and conduct of the study complied with the ethical principles of good clinical practice in accordance with the Declaration of Helsinki and local legal requirements. The study was approved by an independent centralised ethics committee (METOPP, Tilburg, the Netherlands), and by the independent local ethics committee in every participating hospital. Male and female patients aged 18 years or older with a confirmed diagnosis of solid malignancy, planned to receive 2–6 (more) cycles of platinum-based chemotherapy were enrolled. All patients had an Eastern Cooperative Oncology Group (ECOG) performance score of 0–3, a life expectancy of at least 5 months, Hb $\leqslant$ 12.1 g/dL, and were able to understand and provide written informed consent and understand and fill in Dutch language QOL questionnaires. Exclusion criteria included therapy-resistant hypertension, clinically significant dysfunction of any organ system not attributable to the malignancy or chemotherapy that would likely result in early withdrawal from the study, a history of seizures, known hypersensitivity to epoetin alfa or preservatives used in the study medication injection formula, relevant acute or chronic bleeding and evidence of untreated iron, folic acid or vitamin B_{12} deficiencies. Patients who had experienced an acute major illness within 7 days of study entry; major infection within one month of study entry; those who had received androgen therapy within two months of study entry; participated in any other anemia-related trial or a trial involving unlicensed medications/procedures were also not eligible.

Patients were randomised in a 2:1 ratio to receive EPO (Epoetin alfa, Eprex®; Ortho Biotech Europe, a division of Janssen-Cilag [also marketed in the United States as PROCRIT; Ortho Biotech Products, LP]) or best supportive care (BSC). Patients remained to the same allocation throughout the study period. The randomisation code was developed at IKA (Integraal Kanker Centrum Amsterdam) using a computer random number generator to select random permuted blocks of 6 patients. No stratification was performed. After having been provided with written informed consent, the physician called the central randomisation center IKA for assigning treatment. Randomisation was confirmed by a fax message. Neither physicians nor patients were blinded to group assignment.

Enrolled patients with baseline transferrin saturation <20% and/or serum ferritin level <100 ng/ml received oral iron supplements (200 mg elemental iron per day) during the study period. Transfusion of red blood cells (RBCs) was permitted during the study at the discretion of the physician but was to be avoided in patients with Hb $\geqslant$ 9.7 g/dL.

EPO was initiated at 10 000 IU subcutaneously (SC) three times weekly (TIW) for 4 weeks. If after 4 weeks of therapy, Hb had increased by $\geqslant$1.0 g/dL above baseline or Hb level was $\geqslant$12.1 g/dL, EPO was continued at the original dose. If Hb had increased <1.0 g/dL and Hb level was <12.1 g/dL, the dose was increased to 20 000 IU SC TIW. If after another 4 weeks at the higher dose, Hb had increased <1.0 g/dL above baseline and Hb level was still <12.1 g/dL, EPO was discontinued. Patients with Hb > 14 g/dL at any time during the study period did not receive further epoetin alfa until Hb decreased to <13 g/dL, at which point EPO was restarted at a reduced dose of 10 000 IU SC twice weekly. The dose was also reduced to 10 000 IU SC twice weekly if Hb increased >2 g/dL in any 4-week period. Patients who weighed >100 kg received alternating doses of 10 000 IU and 20 000 IU of EPO TIW and dose adjustments were made accordingly. Unless discontinued due to inadequate hematologic response, EPO was administered until 4 weeks after the last cycle of platinum-containing chemotherapy. Patients who did not complete the study period, received EPO until the day of early withdrawal.

2.2. Evaluation of efficacy and safety

The primary efficacy parameter was the proportion of patients transfused during the treatment phase of the study (until 4 weeks after the last administration of platinum-based chemotherapy or the time of early

withdrawal). Secondary efficacy parameters included change in Hb during the study period and change in QOL scores from baseline to end of study. Each of these end points was specified in the original protocol. Transfusion information including number of units RBCs administered was recorded for the 4 weeks preceding study entry and then for the entire study period. Hb evaluations were performed at screening (within 7 days of randomisation), prior to each cycle of chemotherapy, and at study completion or early withdrawal. Data from routine Hb evaluations were also collected. QOL was measured using the Functional Assessment of Cancer Therapy-Anemia (FACT-An) scale and the Cancer Linear Analog Scale (CLAS, also known as the LASA, Linear Analog Scale Assessment) [12,13]. The FACT-An is a 47-item questionnaire consisting of a 27-item general questionnaire, the FACT-G, and a 20-item Anemia subscale. Thirteen of the 20 anemia items comprise a separate Fatigue subscale; the remaining 7-items comprise a Non-Fatigue subscale. The CLAS consists of three linear analog scales, that measure level of energy, the ability to do daily activities, and overall QOL related to cancer symptoms. The FACT-An and CLAS scales are cancer-specific and have demonstrated sensitivity to Hb and therefore were used to detect changes in QOL due to administration of EPO and subsequent increase in Hb [3,4,12,13]. QOL assessments were completed at the start of the study (QOL-baseline), prior to the third chemotherapy cycle since randomisation (QOL-2) and at study end (QOL-end). Safety was evaluated by monitoring adverse events, which were reported by patients spontaneously or in response to questioning by the investigator throughout the study. Adverse events were recorded regardless of their relationship to the drug and rated as mild, moderate, or severe. Survival rates were based on data collected 6 and 12 months after the study completion visit, which took place 4 weeks after the last administration of platinum-based chemotherapy or at the time of early withdrawal.

2.3. Statistical analyses

The study had a target sample size of 300 patients (200 in the EPO and 100 in the BSC group). The sample size provided 80% power to detect a 15% reduction in the proportion of patients with at least one transfusion during the study period at a significance level of 5%. The sample size anticipated that approximately 30% of patients would withdraw from the study early. Two populations were designated for purposes of intent-to-treat (ITT) analyses: a safety population (all randomised patients for whom safety data were available) and an efficacy population (patients for whom efficacy data were available from at least one time point after randomization, ITT population). Adverse events were monitored in the safety population, and all efficacy end points were analysed for the ITT efficacy population. Shifts in continuous or ordinal parameters were analysed using the Wilcoxon signed rank test. For all analyses, $P < 0.05$ was considered statistically significant. The protocol was not designed or powered for survival. However, survival distributions were estimated by Kaplan–Meier curves, which were compared by means of log-rank tests.

3. Results

From November 1999 to December 2002 a total of 316 patients were enrolled. Follow-up visits for survival assessment took place from November 2000 to May 2004. One patient (BSC group) withdrew informed consent immediately after randomisation and was excluded from both safety and efficacy analyses. Two other patients (BSC group) were excluded from the efficacy analysis. One patient died, and one patient withdrew informed consent, both before any efficacy data had been obtained. The ITT safety population thus consisted of 315 patients and the ITT efficacy population of 313 patients.

3.1. Demographics and baseline characteristics

Demographic and baseline characteristics of the ITT efficacy population are listed in Table 1. Most baseline characteristics were well balanced between the two groups. There was however a higher incidence of metastatic disease (78% *vs.* 61%, EPO *vs.* BSC, $P = 0.001$) and higher ECOG performance scores in the EPO group (mean score 1.1 *vs.* 0.9, EPO *vs.* BSC, $P = 0.015$). The most commonly used chemotherapy regimen was the combination of gemcitabine and cisplatin (37% and 43% in the EPO and BSC group, respectively), followed by carboplatin and paclitaxel (16% and 15% in EPO and BSC group, respectively). Patients were on study for a mean period of 13.9 *vs.* 14.5 weeks (EPO *vs.* BSC, $P = 0.330$).

3.2. Hemoglobin responses

Fig. 1 illustrates the change in hemoglobin over time in the two groups. Of the 313 ITT efficacy patients, 304 were evaluated for change in Hb. Nine patients were excluded from the analysis, due to missing data on Hb at baseline ($n = 2$) or on Hb after baseline ($n = 7$). In the EPO group ($n = 197$), mean Hb increased from 10.7 to 12.3 g/dL ($P < 0.001$), whereas in the BSC group ($n = 94$) it decreased from 10.8 to 10.4 g/dL ($P < 0.001$) ($P < 0.001$, EPO *vs.* BSC). In 13 patients, data on Hb at last visit were lacking. As an additional measure of efficacy, the proportion of responders (patients who

Table 1
Baseline demographics and clinical characteristics

Characteristic	EPO (n = 211)	BSC (n = 104)
Sex, n (%)		
Male	117 (55)	61 (59)
Female	94 (45)	43 (41)
Age, years, mean ± SD (range)	57 ± 11 (20–80)	58 ± 10 (27–78)
Race, n (%)		
White	200 (95)	103 (99)
Asian	5 (2)	0
Black	1 (1)	1 (1)
Other	5 (2)	0
ECOG performance status, mean ± SD	1.1 ± 0.6*	0.9 ± 0.7
Primary site of malignancy, n (%)		
NSCLC	54 (26)	23 (22)
SCLC	14 (7)	5 (5)
Upper GI tract[a]	51 (24)	29 (28)
Gynecologic[b]	36 (17)	23 (22)
Other[c]	56 (26)	24 (23)
Missing	0	1 (1)
Metastatic disease, n (%)		
Yes	165 (78)**	63 (61)
No	46 (22)**	41 (39)
Hb, g/dL (mean ± SD)	10.7 ± 1.0 (7.6–13.8)	10.8 ± 1.0 (8.5–12.7)
Transfused 4 weeks prestudy, n (%)	23 (11)	11 (11)
Chemotherapy regimens, n (%)		
Gemcitabine/cisplatin	79 (37)	45 (43)
Carboplatin/paclitaxel	33 (16)	16 (15)
Carboplatin/gemcitabine	22 (10)	7 (7)
Other cisplatin-containing	53 (25)	25 (24)
Other carboplatin-containing	12 (6)	5 (5)
Oxaliplatin-containing	12 (6)	6 (6)

EPO, epoetin alfa; BSC, best supportive care; SD, standard deviation; ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small-cell lung cancer; SCLC, small-cell lung cancer; GI, gastrointestinal; Hb, hemoglobin.

[a] Includes gastric cancer and esophageal cancer.

[b] Includes ovarian cancer, cervical cancer, and cancer of the uterine tube.

[c] All other primary tumor types each represent <7% of patients; calculation includes 10 tumors (8 EPO, 2 BSC) of unknown origin.

* $P = 0.015$ *vs.* BSC.

** $P = 0.001$ *vs.* BSC.

achieved a $\geqslant$2 g/dL increase in Hb unrelated to transfusion, i.e. no transfusion within 28 days before measurement), correctors (patients who achieved a Hb$\geqslant$12 g/dL unrelated to transfusion) and hematopoietic responders (correctors or responders) was determined. The EPO group, compared with the BSC group, had a significantly greater percentage of responders (69% *vs.* 31%, $P < 0.001$), correctors (67% *vs.* 30%, $P < 0.001$) and hematopoietic responders (76% *vs.* 45%, $P < 0.001$) (Table 2).

3.3. Transfusion requirements

In addition to achieving higher Hb during the study period, the EPO group also exhibited a lower transfusion rate, as listed in Table 3. In the ITT efficacy population, a significantly smaller proportion of patients in the EPO (36%) *vs.* the BSC (65%) group were transfused during the study period ($P < 0.001$). Results were comparable when transfusions within 4 weeks after randomisation were excluded from the analysis (23 *vs.* 52%, EPO *vs.* BSC, $P < 0.001$). An advantage was also observed for EPO over BSC for two other transfusion-related end-points: the mean number of units transfused was lower (1.5 units *vs.* 3.1 units, $P < 0.001$) and the time to first transfusion or low Hb (<9.7 g/dL) was significantly longer (99 *vs.* 43 days, $P < 0.001$).

3.4. Quality of life

Of the 313 ITT efficacy patients, 213 (150 randomised to EPO and 63 to BSC) were evaluated for changes in CLAS scores, and 220 patients (155 randomised to EPO and 65 to BSC) were evaluated for changes in FACT-An score. Only patients who completed the QOL questionnaire at baseline and at QOL-2 and/or

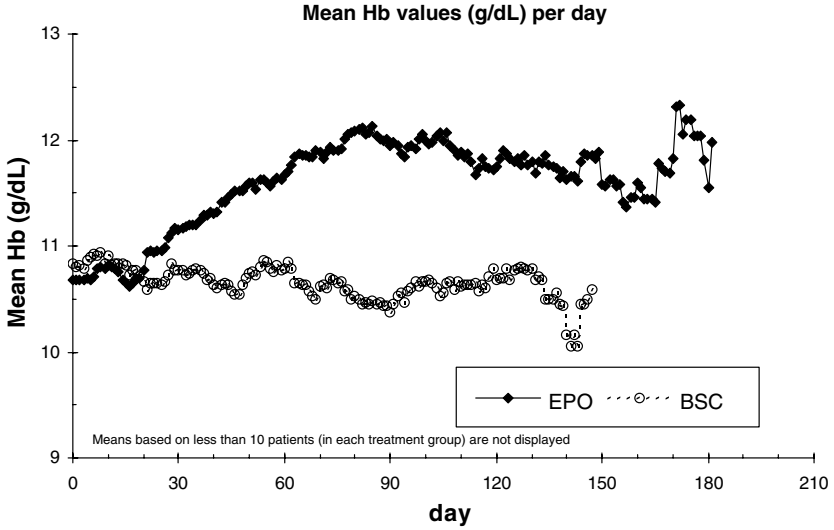


Fig. 1. Mean daily hemoglobin levels for all patients treated with epoetin alfa or best supportive care (ITT population; epoetin alfa *vs.* best supportive care). Means based on values from less than 10 patients (in each treatment group) are not displayed.

Table 2
Patient hematological response

	EPO (n = 208) n, %	BSC (n = 100) n, %	Difference (95% CI) %	P-value
Responder[a]	143 (69)	31 (31)	39 (27–49)	<0.001
Corrector[b]	139 (67)	30 (30)	37 (26–48)	<0.001
Hematopoietic responder[c]	158 (76)	45 (45)	31 (20–42)	<0.001

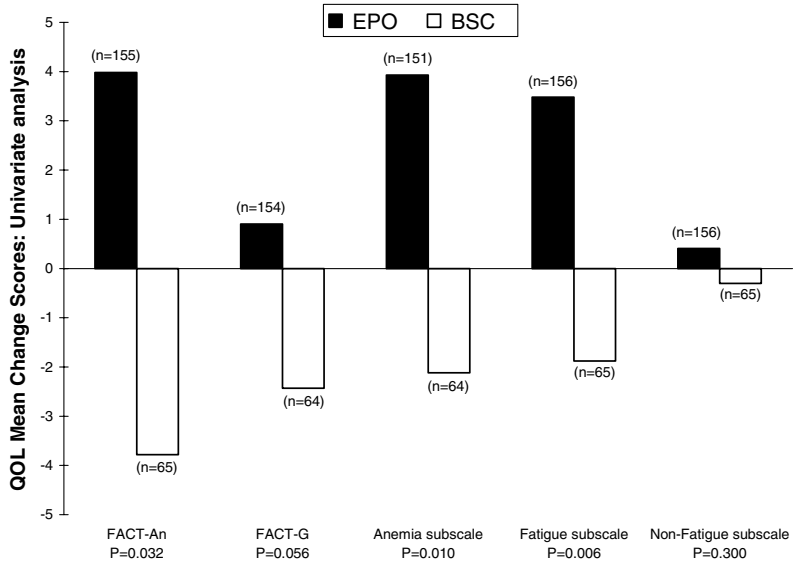
CI, confidence interval.
[a] Hb increase $\geqslant$2 g/dL, unrelated to transfusion (i.e. no transfusions in previous 4 weeks).
[b] Hb > 12 g/dL, unrelated to transfusion.
[c] Corrector or responder; Hb increase $\geqslant$2 g/dL or Hb > 12 g/dL, unrelated to transfusion.

Table 3
Patients requiring transfusion

	EPO (n = 211)	BSC (n = 102)	Difference (95% CI) %	P-value
Patients transfused				
Study period, n (%)	77 (36)	66 (65)	28 (17–40)	<0.001
First 4 weeks excluded, n (%)	49 (23)	53 (52)	29 (17–40)	<0.001
Total units transfused				
Study period, mean (SD)	1.5 (2.6)	3.1 (3.1)	1.6 (0.9–2.3)	<0.001
First 4 weeks excluded, mean (SD)	1.0 (2.2)	2.1 (2.5)	1.1 (0.5–1.7)	<0.001
Time to first transfusion[*]				
Study period, days (SD)	99 (6)	43 (4)	56 (55–57)	<0.001
First 4 weeks excluded, days (SD)	108 (6)	40 (3)	68 (67–69)	<0.001

CI, confidence interval; SD, standard deviation.
[*] or Hb < 9.7 g/dL.

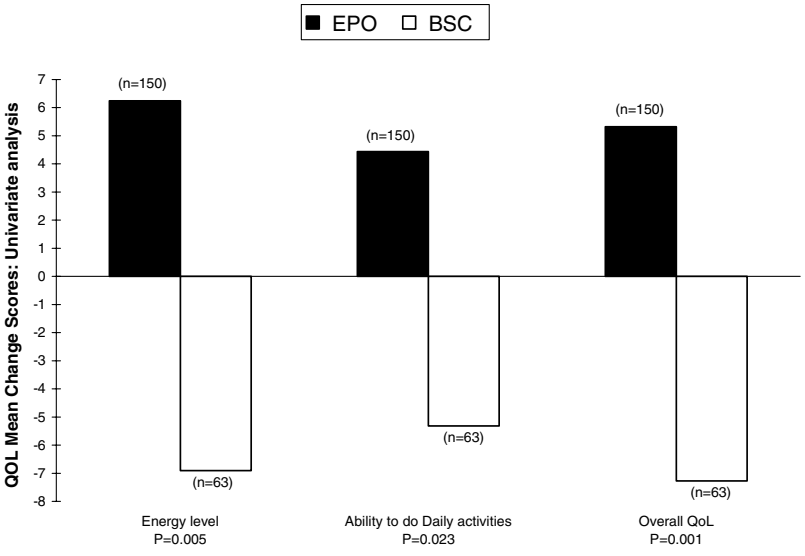
at QOL-end were included in the analysis. Scores at baseline were comparable between groups for every QOL domain investigated. Mean change scores (QOL-end *vs.* QOL-baseline) for 8 cancer- and anemia-specific QOL scales are shown in Figs. 2 and 3. Significant differences for EPO over BSC were found for 6 QOL scales (Fact-An, FACT-An Anemia subscale, FACT-An Fatigue subscale, and the 3 CLAS subscales, range, P = 0.001–0.032). The statistically significant differences between the two groups were marked by improvement in the EPO group and deterioration in the BSC group. Difference in mean change QOL score for EPO over BSC did not reach significance for 2 QOL scales, the FACT-An Non-Fatigue subscale (P = 0.300) and the FACT-G (P = 0.056), although significance was achieved on the FACT-G sub-domains physical and



	EPO			BSC					
								95% CI	
	Mean	s.d.	n	Mean	s.d.	n	Diff. mean	Lower limit	Upper limit
FACT-An	3.98	26.75	155	-3.69	24.38	65	7.67	0.30	15.08
FACT-G	0.90	10.94	154	-2.52	10.95	64	3.42	0.17	6.67
Anemia subscale	3.93	15.63	151	-1.91	14.66	64	5.84	1.38	10.30
Fatigue subscale	3.48	12.67	156	-1.67	11.61	65	5.15	1.63	8.67
Non-Fatigue subscale	0.41	3.81	156	-0.31	4.21	65	0.72	-0.49	1.93

s.d., standard deviation; Diff.mean, difference of the means (EPO versus BSC); C.I., confidence interval.

Fig. 2. Comparison of QOL (FACT-An, FACT-G, Anemia subscale, Fatigue subscale and Non-Fatigue subscale) mean change scores by treatment group (epoetin alfa *vs.* best supportive care).



	EPO			BSC					
								95% CI	
	Mean	s.d.	n	Mean	s.d.	n	Diff. mean	Lower limit	Upper limit
Energy level	6.2	25.3	150	-6.9	29.6	63	13.1	4.6	21.6
Ability to do Daily activities	4.4	26.8	150	-5.3	28.0	63	9.7	1.4	18.0
Overall QoL	5.3	24.1	150	-7.3	27.8	63	12.6	4.6	20.6

s.d., standard deviation; Diff.mean, difference of the means (EPO versus BSC); C.I., confidence interval.

Fig. 3. Comparison of QOL (CLAS comprising of energy level, ability to do daily activities and overall QOL) mean change scores by treatment group (epoetin alfa *vs.* best supportive care).

functional well being ($P = 0.005$ and 0.021, respectively, data not shown).

3.5. Safety evaluation

EPO was well tolerated. The overall incidence of adverse events and the incidence of individual adverse events were generally similar between the two treatment groups (Table 4). The most common adverse events were nausea, fatigue, vomiting, constipation, diarrhea and fever, which were probably associated with chemotherapy treatment. Pure red-cell aplasia has not been observed in oncology patients, and there were no observed instances in the current study either. Hypertension was reported in 7 patients (3.3%) in the EPO group and 3 patients (2.9%) in the BSC group ($P = 1.000$). Hypertension was not considered to be related to epoetin therapy in any of the patients. Seven patients (3.3%) in the EPO group experienced a thromboembolic event (2 patients experienced two events) *vs.* 1 patient (1.0%) in the BSC group ($P = 0.28$). The only thromboembolic event that was considered to be possibly related to epoetin alfa concerned a patient who experienced a deep venous thrombosis after having achieved a Hb increase of 2.2 g/dL within 3 weeks. Three patients in the EPO group experienced a cerebrovascular accident or transient ischemic attack (1.4% *vs.* 0%, EPO *vs.* BSC, $P = 0.31$) and 4 patients experienced seizures or epileptiform attacks (1.9% *vs.* 0%, EPO *vs.* BSC, $P = 0.55$) which were not considered to be related epoetin therapy.

Table 4
Incidence of most common adverse events

Adverse event, *n* (%)	EPO ($n = 211$)	BSC ($n = 104$)
Any adverse event	197 (93)	101 (97)
Nausea	63 (31)	32 (32)
Fatigue	53 (27)	36 (36)
Vomiting	45 (23)	29 (29)
Constipation	34 (17)	26 (26)
Diarrhea	37 (19)	20 (20)
Fever	36 (18)	17 (17)
Distal paresthesia	34 (17)	15 (15)
Dizziness	30 (15)	17 (17)
Headache	34 (17)	11 (11)
Pain	28 (14)	13 (13)
Coughing	25 (13)	13 (13)
Leucopenia	22 (11)	8 (8)
Dyspnoe	17 (9)	11 (11)
Thrombopenia	22 (11)	6 (6)
Influenza-like symptoms	21 (11)	5 (5)

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

3.6. Survival

Survival was assessed 6 and 12 months after study completion. At the 12-month assessment, 113 patients (73 [35%] receiving EPO and 40 [38%] receiving BSC) were alive; 192 patients (131 [62%] receiving EPO and

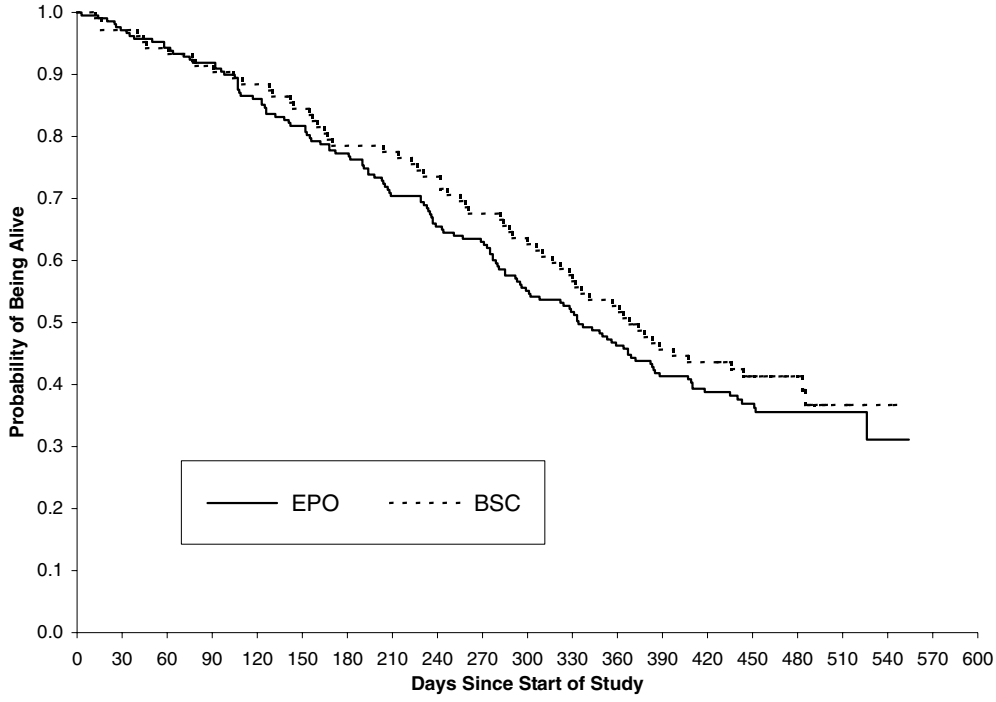


Fig. 4. Kaplan–Meier estimate of survival at 12-month follow-up (safety population). No difference in estimated survival rates, $P = 0.39$ by log-rank test (epoetin alfa *vs.* best supportive care).

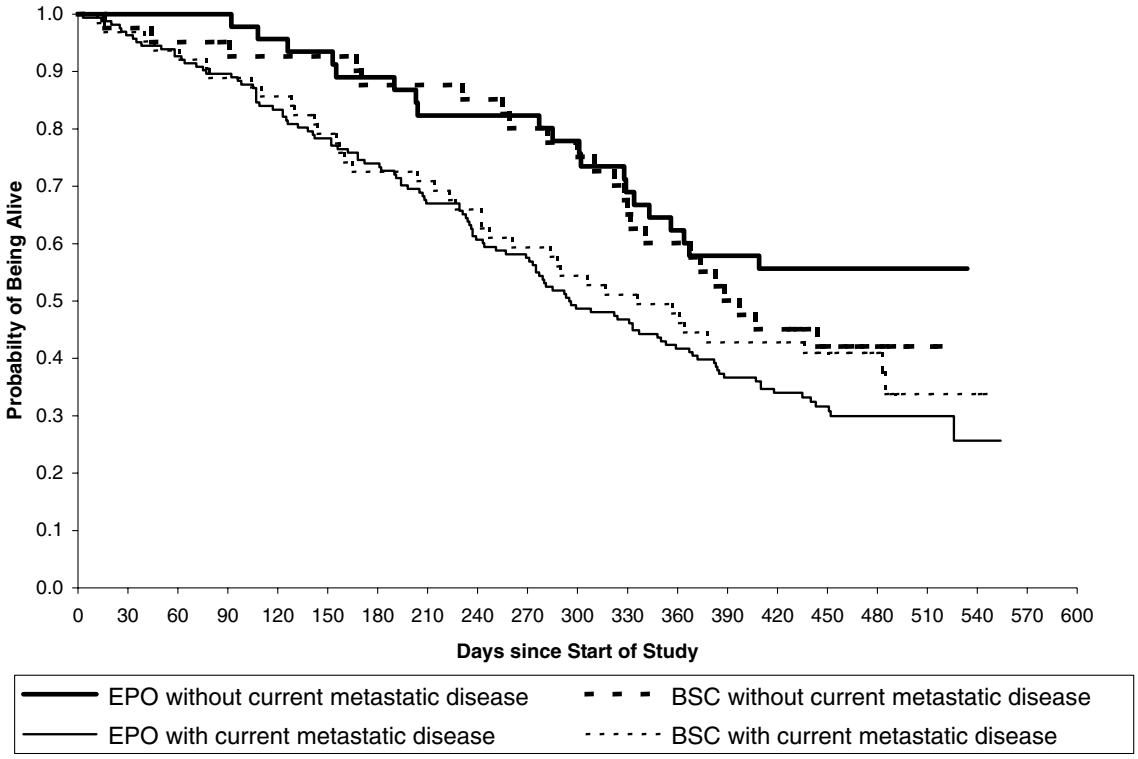


Fig. 5. Kaplan–Meier estimate of survival at 12-month follow-up by metastatic disease. No difference in estimated survival rates by log-rank test (patients without metastatic disease, $P = 0.3331$; patients with metastatic disease, $P = 0.3513$; epoetin alfa *vs.* best supportive care).

61 [59%] receiving BSC) had died, and 10 (7 [3%] receiving EPO and 3 [3%] receiving BSC) were lost to follow-up. Median survival times were 334 days (11 months) in the EPO group and 368 days (12 months) in the BSC group (Fig. 4; $P = 0.39$). As expected, patients with metastatic disease had a higher mortality rate within the follow-up period compared to patients without metastatic disease (Fig. 5), but there were no significant differences with respect to survival rates between the 2 treatment groups in these subsets of patients.

4. Discussion

Several large community and double-blind placebo controlled, randomised trials have demonstrated the therapeutic benefit of EPO [3,11,14–17]. The studies assessing QOL documented a strong correlation between increase in Hb and improvement in QOL [11,15]. Most of these studies however, focused on anemia correction and recruited patients with Hb < 10.5–11 g/dL. Based on current clinical evidence, ASCO/ASH guidelines for the use of epoetin during chemotherapy recommend the use of EPO as a treatment option for patients with chemotherapy-associated anemia with Hb < 10 g/dL. For patients with less severe anemia (Hb < 12 g/dL) the use of EPO should be determined by clinical circumstances [5]. The results of the current study add strong evidence supporting the use of epoetin at Hb 10–12 g/dL to improve hematologic outcomes and QOL in patients with solid malignancies receiving platinum-based chemotherapy. EPO therapy resulted in a significant reduction in the proportion of patients requiring transfusions (36% *vs.* 65%, EPO *vs.* BSC, $P < 0.001$). Despite the lower transfusion rate, mean Hb in the EPO group increased from 10.7 at baseline to 12.3 g/dL at study end, whereas it decreased from 10.8 to 10.4 g/dL in the BSC group. In addition to the efficacy of EPO with respect to transfusion requirements and hemoglobin response, the present study demonstrates a strong positive effect of EPO on QOL. Our data are supported by a recently published study of EPO (40 000 IU once weekly) *vs.* standard of care in 354 breast cancer patients with Hb $\leqslant$ 12 g/dL during myelotoxic chemotherapy [7].

However, basic and clinical research has raised questions about the role of epoetin therapy in tumor progression. Preclinical evidence has suggested a possible role of erythropoietin in tumor development and tumor growth. Erythropoietin and erythropoietin receptor expression have been detected in human tumors and cancer cell lines. The administration of recombinant human erythropoietin has been shown to result in enhanced growth of human cancer cell lines *in vitro* [18–20]. Two clinical trials that were published shortly before the completion of the present study, have

suggested a negative effect of epoetin on survival in cancer patients [21,22]. The first was a randomised, double-blind, placebo-controlled study performed in metastatic breast cancer patients who received epoetin alfa from Hb < 12 g/dL. This study was terminated early after observing a significantly lower 12-month survival rate in the group treated with epoetin alfa (70% *vs.* 76%, epoetin alfa *vs.* placebo, $P = 0.012$). The observed difference was due mainly to an increased mortality in the first 4 months of the study caused by an increased incidence of disease progression (6% *vs.* 3%) and thrombotic and vascular events (1% *vs.* 0.2%). In his article in Lancet Oncology, the principal investigator urged that caution be used in interpreting these results as the study was not designed to prospectively collect data on many potential prognostic survival factors that may have affected the study outcome. A retrospective chart review suggested that patients randomised to the epoetin alfa group were more likely to have adverse factors such as advanced age, lower performance status, greater extent of disease at study entry, and more risk factors for thromboembolic events [21]. The second study was a randomised double-blind, placebo-controlled trial in head and neck cancer patients receiving curative radiotherapy. Patients received subcutaneous epoetin beta 300 IU/kg thrice weekly or placebo from Hb < 12 g/dL in women to Hb < 13 g/dL in men. The end-point of demonstrating that epoetin when used in anemic head and neck cancer patients receiving radiotherapy could act as radiosensitiser was not met. In fact, poorer loco regional progression-free survival was observed in the epoetin beta group *vs.* the placebo group. In subgroup analyses, epoetin beta was related to a significantly poorer outcome only among patients younger than 60 years, in patients in with baseline Hb > 11 g/dL, and among patients who had advanced disease or cancer of the hypopharynx. However, among patients with cancer of the hypopharynx (22% of epoetin beta treated patients), a higher proportion of the patients that received epoetin beta had unfavorable baseline characteristics, such as relapses at baseline and stage IV disease [22]. The higher percentage of smokers in the epoetin beta treated patients may also have negatively affected survival in this group since smoking during radiotherapy could effect survival in patients with head and neck cancer [23]. In the present study there were no significant differences in patient survival between the EPO and BSC group, despite a higher proportion of patients with metastatic disease and poor performance status in the EPO group. Although the percentage of thromboembolic events; cerebrovascular accidents and transient ischemic attacks; and seizures and epileptiform attacks were apparently higher in the EPO group than in the BSC group, the percentages were small and not significantly different.

We conclude that early intervention with epoetin alfa has a favorable, statistically significant effect on transfusion requirements, Hb and QOL, in patients with mild to moderate anemia. Further research is required to study the effect of epoetin therapy on survival, tumor progression and the incidence of thrombovascular events.

Conflict of interest statement

None declared. One of the authors, Mr. Wormhoudt LW, PhD, has competing interests as he is an employee of Ortho Biotech, a division of Janssen-Cilag B.V.

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