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Is there a possible survival benefit to increasing hemoglobin levels with epoetin alfa during chemotherapy?

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Abstract

Anemia is common in cancer patients during chemotherapy. The study discussed in this article was primarily designed to assess the effects of epoetin alfa on transfusion requirements, hematopoietic response, quality of life (QOL), and safety in cancer patients receiving nonplatinum–based chemotherapy under randomized, double-blind, placebo-controlled conditions. Over the course of the study, a growing body of evidence from other studies suggested an association between low hemoglobin (Hb) levels and poorer prognosis in patients receiving radiotherapy, chemotherapy or combination therapies. Therefore, prior to unblinding, the study protocol was amended to explore a possible relationship between increased Hb levels and survival by collecting survival data for 12 months after the last patient completed the study. A total of 375 patients with solid tumors or nonmyeloid hematologic malignancies (Hb $\leqslant$10.5 g/dl or Hb $>$10.5 g/dl but $\leqslant$12.0 g/dl with a decrease of $\geqslant$1.5 g/dl per cycle or month since starting chemotherapy) were randomized 2:1 to receive 150–300 IU/kg epoetin alfa ($n=251$) or placebo ($n=124$) subcutaneously three times weekly for 12–24 weeks, or for 3–6 chemotherapy cycles plus 4 weeks after chemotherapy. The primary efficacy endpoint was the proportion of patients transfused. Secondary endpoints included changes in Hb level and QOL measurements. Hematopoietic response in terms of the proportion of responders (patients whose Hb level increased by at least 2 g/dl during the study without transfusion) and correctors (patients who achieved an Hb level of at least 12 g/dl during the study without transfusion) were also determined. Compared with placebo, epoetin alfa significantly decreased transfusion requirements ($P=0.0057$) and increased Hb levels ($P<0.001$). There were significantly more responders and correctors in the epoetin alfa group than in the placebo group ($P<0.001$ for both). Epoetin alfa also provided significantly greater improvements ($P<0.01$) in all primary cancer- and anemia-specific QOL domains, including energy level, ability to do daily activities, fatigue and overall QOL score. Adverse events were comparable between treatment groups. Median survival times were 17 months for epoetin alfa–treated patients and 11 months for placebo-treated patients. Kaplan-Meier 12-month survival estimates were 60% for epoetin alfa-treated patients and 49% for placebo-treated patients. The log-rank test indicated a trend in overall survival for epoetin alfa ($P=0.13$). These survival results must be interpreted with caution because the study was not powered to assess survival, nor was it controlled for stage of disease, bone marrow involvement, intensity of chemotherapy or disease progression. This study allowed regulatory approval of epoetin alfa for treatment of non-cisplatin–induced chemotherapy-related anemia. Epoetin alfa also decreases the impact of anemia on QOL, and may improve survival of cancer patients.

Keywords: Anemia; Chemotherapy; Epoetin alfa; Quality of life; Tumor hypoxia

1. Introduction

Low hemoglobin (Hb) levels are common in cancer patients and have been linked to poorer prognosis in patients at diagnosis and in those receiving radiotherapy or chemotherapy [1–4]. Prior research suggests that increased Hb levels are associated with improved treatment outcomes [1,2]. This may be partially explained by studies showing that tumor hypoxia contributes to the malignancy of cancer and that delivery of oxygen to the tumor is important in the response to cancer treatment [5–8]. In addition, a preclinical study of the differential toxicity of antineoplastic therapies toward oxygenated

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and hypoxic tumor sub-populations *in vivo* conducted in murine fibrosarcoma indicated that cells located distally from the tumor vasculature were significantly less affected by most anticancer agents [9]. Retrospective comparisons indicate that correcting anemia may improve the response to concomitant chemotherapy or radiotherapy and may influence patient survival after radiotherapy [2,10].

In addition to its effects on clinical outcomes, anemia has a significant and meaningful impact on quality of life (QOL). Effective management of anemia has resulted in marked improvements in energy level, ability to do daily activities, and overall QOL scores in several studies [11–16]. These effects on QOL were seen when the final Hb levels were increased from 1.8 to 2.0 g/dl over baseline levels of 9.2–9.5 g/dl [12–16]. These studies support the idea that Hb levels should be increased to at least 11 g/dl for effective management of anemia. Detailed analyses confirmed that the greatest increase in QOL scores is seen as the Hb increases to 11–12 g/dl [17].

The effects of improving anemia on the patient's QOL may be independent of disease response, tumor type and clinical outcomes [14]. Thus, QOL changes should be considered independently as elements of the functional status of cancer patients.

The initial purpose of the study discussed in this paper, conducted by Littlewood *et al*. [16] was to assess the effects of recombinant human erythropoietin (rHuEPO, epoetin alfa) on transfusion requirements, Hb level, QOL and safety in patients receiving nonplatinum–based chemotherapy under randomized, double-blind, placebo-controlled conditions [16]. Over the course of the study, the aforementioned growing body of evidence from other studies suggested an association between low Hb levels and poorer prognosis in patients receiving radiotherapy, chemotherapy and combination radiochemotherapy. Therefore, prior to unblinding, the study protocol was amended to explore a possible relationship between increased Hb levels and survival [16]. This study has provided justification for QOL assessments during cancer therapy as well as laid the foundation for subsequent studies that have examined the clinical significance of improvements in QOL with reference to elevated Hb levels.

2. Patients and methods

A detailed description of study methods has been presented elsewhere [16]. Briefly, this study was a multinational, multicenter, double-blind, placebo-controlled, randomized trial including 375 patients aged 18 years or older. Inclusion criteria were: receiving or scheduled to receive nonplatinum–based chemotherapy for solid tumor or non myeloid hematologic malignancy; Hb $\leqslant$10.5 g/dl or $>$10.5 g/dl but $\leqslant$12.0 g/dl after a $\geqslant$1.5 g/dl decrease per month or cycle since starting chemotherapy; and a life expectancy of $\geqslant$6 months. All patients gave written informed consent prior to entering the study. The study protocol and amendments were reviewed by an independent ethics committee.

The treatment schedule is summarized in Fig. 1. Patients were randomized 2:1 to receive 150 IU/kg epoetin alfa or a matching volume of placebo subcutaneously three times weekly for a maximum of 28 weeks of study treatment, which included 12–24 weeks (3–6 cycles) of chemotherapy and a 4-week period after chemotherapy. (Outside of the United States, epoetin alfa is manufactured by Ortho Biologics, LLC, and distributed and marketed as EPREX® or ERYPO® by Ortho Biotech and Janssen-Cilag. In the United States, PROCRIT® [epoetin alfa] is manufactured by Amgen Inc. and distributed and marketed by Ortho Biotech Products, L.P.)

The primary efficacy endpoint was the proportion of patients transfused after the first 4 weeks of treatment. Secondary endpoints included change in Hb level from baseline to last assessment and change in QOL parameters from baseline to last assessment. Quality of life was assessed by the Cancer Linear Analog Scale (CLAS, also known as the Linear Analog Scale Assessment, or LASA) for assessment of energy levels, ability to do daily activities, and overall QOL, and the Anemia and Fatigue subscales of the Functional Assessment of Cancer Therapy-Anemia (FACT-An) scale.

The proportion of responders (patients whose Hb level increased by at least 2 g/dl during the study without transfusion 30 days prior) and correctors (patients who achieved an Hb level of at least 12 g/dl during the study without transfusion 30 days prior) were also determined. Transfusion-related Hb values on study were excluded from the determination of responders and correctors. The proportion of responders and correctors was calculated for patients who were on study for at least 28 days.

Data for the prospective analysis of survival, including date and cause of death, were collected 12 months following study end, i.e. 12 months after the last patient ended the study period. Survival distributions were estimated with Kaplan–Meier curves, which were compared by means of log-rank tests. To compensate for the variable survival times associated with different malignancies, Kaplan–Meier estimates of survival by tumor strata (solid versus hematologic) were also performed. Further analysis with the Cox regression model was performed using a stepwise selection procedure to correct for effects of potential prognostic factors on patient survival [18]. Four significant factors—tumor stratum, baseline Hb level, age and area under the curve (AUC) for neutrophils—were included in the model.

For all statistical analyses, $P < 0.05$ was considered significant. Subgroups had no P values computed.

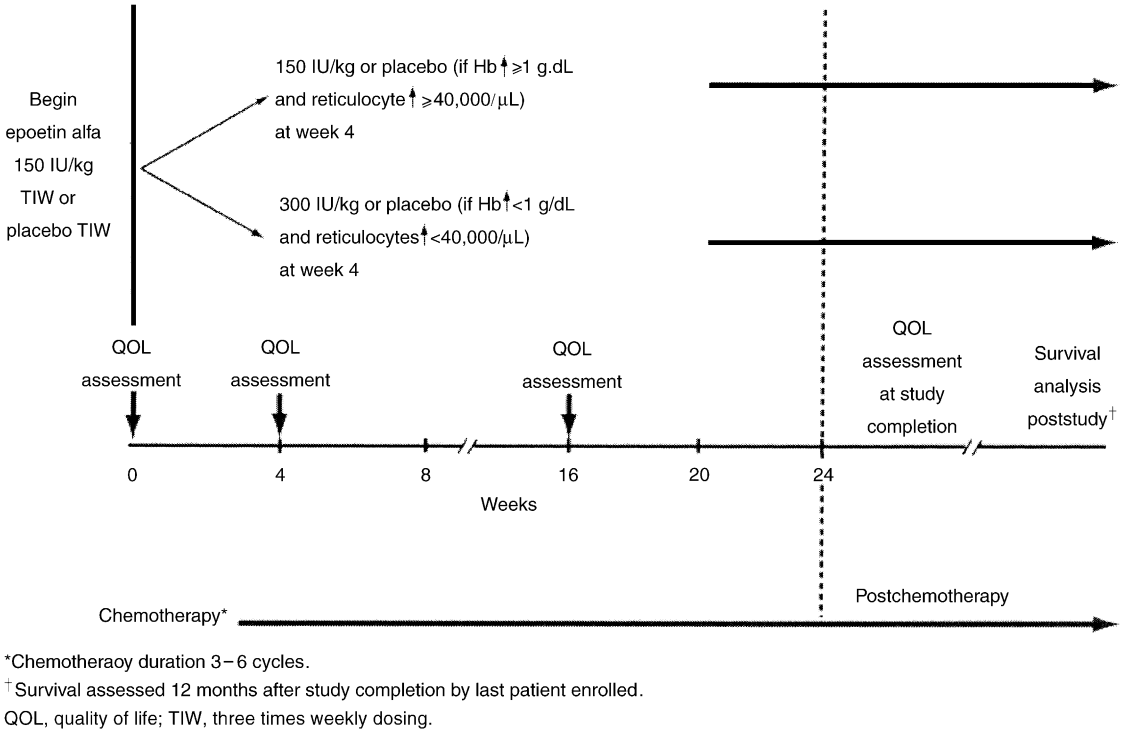

Fig. 1. Treatment schema. Patients received 150 IU/kg epoetin alfa unless Hb had increased <1 g/dl or reticulocytes had increased <40 000/μl at week 4. The duration of chemotherapy was 3–6 cycles. Patient survival was assessed 12 months after the completion of the last patient enrolled in the study.

Table 1
Intent-to-treat patient baseline demographics of the treatment groups

Description	Epoetin alfa ($n=251$)	Placebo ($n=124$)
Gender		
Male	85 (34%)	39 (31%)
Female	166 (66%)	85 (69%)
Age (year)[a]	58.3±14.2	59.5±13.9
Time since diagnosis (days)[a]	35.3±47.4	31.1±40.3
Hb (g/dl)[a]	9.9±1.1	9.7±1.1
Prestudy transfusions	71 (28%)	44 (36%)
Received chemotherapy within 3 months of study	231 (92%)	114 (92%)

Adapted and reprinted with permission [16].
[a] Mean ±S.D.

Table 2
Tumor types of treatment groups

Malignancy	Epoetin alfa ($n=251$)	Placebo ($n=124$)
Solid tumor	136 (54%)	66 (53%)
Breast	78 (31%)	36 (29%)
Other	58 (23%)	30 (24%)
Hematologic tumor	115 (46%)	58 (47%)
Non-Hodgkin's lymphoma	41 (16%)	21 (17%)
Multiple myeloma	37 (15%)	25 (20%)
Other	37 (15%)	12 (10%)

Adapted and reprinted with permission [16].

3. Results

The demographics of the patient population are summarized in Table 1; epoetin alfa and placebo groups were demographically similar at baseline. The tumor types associated with the treatment groups are described in Table 2.

As shown in Fig. 2, epoetin alfa significantly decreased transfusion requirements ($P=0.0057$). This decrease in the proportion transfused was observed in patients with both solid and hematologic tumors. Since the epoetin alfa and placebo groups had comparable proportions of malignancies (Table 2), we can conclude that the differences in transfusion requirements illustrated in Fig. 2 were not likely to be due to tumor types but were due to treatment differences. These results suggest that over the treatment range of 150–300 IU/kg, epoetin alfa decreases the need for anemia-induced blood transfusions.

In addition to the effect of epoetin alfa on the transfusion requirements, epoetin alfa also increased mean Hb levels ($P<0.001$), as shown in Fig. 3. The time course of this effect (Fig. 3) indicates that Hb levels increased for the first 10–14 weeks on epoetin alfa

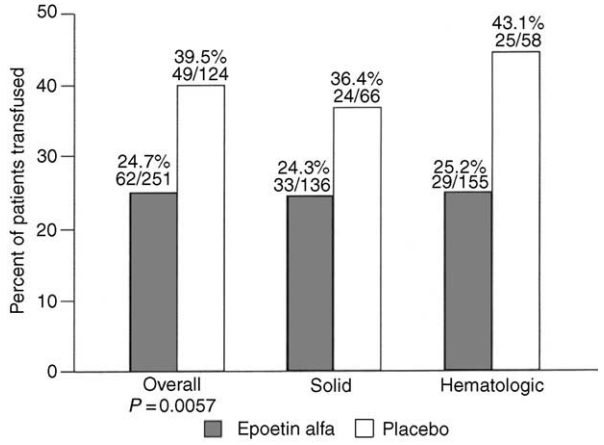

Fig. 2. Epoetin alfa decreases the proportion of patients transfused after day 28. The proportion of patients receiving a transfusion to correct for chemotherapy-induced anemia, the primary study endpoint, was determined for the intent-to-treat (ITT) population.

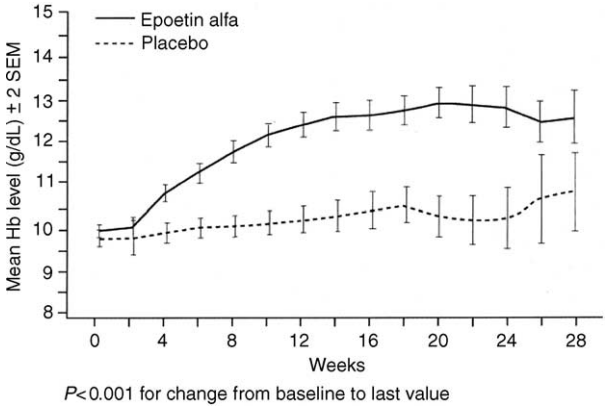

Fig. 3. Epoetin alfa improves haemoglobin levels. The mean Hb levels of the epoetin alfa (—) and placebo (- - -) populations are plotted as a function of time after the start of the study. Error bars indicate ±2 standard errors. The 28-week values for the efficacy (EFF) population and placebo groups differ with $P < 0.001$. Reprinted with permission [16].

therapy, while the Hb levels in the placebo group did not significantly differ from baseline over the same period. After 28 weeks, the mean Hb level of the epoetin alfa group had increased by 2.2±2.18 g/dl ($P < 0.001$), while the placebo group had increased only 0.5±1.79 g/dl (Fig. 3). The hematopoietic effect of epoetin alfa is likely an important factor contributing to the decreased transfusion requirements of this treatment group. Furthermore, the epoetin alfa–induced increases in Hb were of the magnitude where QOL improvements would be anticipated [12–15].

Overall, there were significantly more responders in the epoetin alfa group (70.5%) than in the placebo group (19.1%) ($P < 0.001$) (Table 3). This effect was maintained when an evaluation of the proportion of responders by tumor type (solid or hematologic) and Hb stratum (⩽10.5 g/dl or >10.5 g/dl) was performed

Table 3
Proportion of responders[a] (efficacy population)

Response	Epoetin alfa ($n = 244$)	Placebo ($n = 115$)	P value[b]
Responder	172 (70.5%)	22 (19.1%)	<0.001
Non-responder	72 (29.5%)	93 (80.9%)	

[a] Patients whose hemoglobin increased by ⩾2 g/dl unrelated to transfusions.
[b] Fisher exact test.

Table 4
Proportion of responders[a] by sub group (efficacy population)

Sub group	Epoetin alfa ($n = 244$)	Placebo ($n = 115$)
Tumor type		
Solid	87/131 (66.4%)	13/61 (21.3%)
Hematologic	85/113 (75.2%)	9/54 (16.7%)
Hemoglobin stratum		
⩽10.5 g/dl	139/203 (68.5%)	22/100 (22.0%)
>10.5 g/dl	33/41 (80.5%)	0/15 (0.0%)

[a] Patients whose hemoglobin increased by ⩾2 g/dl unrelated to transfusions.

(Table 4). Among responders, the mean study day on which an Hb level at least 2 g/dl above baseline was reached was earlier for the epoetin alfa group (52 days) than the placebo group (75 days). In addition, the maximum mean Hb level reached among responders was higher in the epoetin alfa group (14.2 g/dl) than in the placebo group (12.2 g/dl).

Overall, there were significantly more correctors in the epoetin alfa group (67.6%) than in the placebo group (15.7%) ($P < 0.001$) (Table 5). This effect was maintained upon evaluation of correctors by tumor stratum (solid or hematologic) and Hb stratum (⩽10.5 g/dl or >10.5 g/dl) (Table 6). Within the epoetin alfa group, the proportion of correctors was slightly higher in patients with hematologic malignancies than in patients with solid tumors, as well as in patients in the higher Hb stratum. Among correctors, the mean study day on which an Hb level of at least 12 g/dl was reached was earlier for the epoetin alfa group (52 days) than the placebo group (80 days).

As a means of evaluating the effect of epoetin alfa on the QOL of the patients, cancer- and anemia-specific QOL domains, including energy level, ability to do daily activities, fatigue, anemia and overall QOL scores were determined. As shown in Figs. 4 and 5, epoetin alfa significantly increased the patients' energy, ability to do daily activities, fatigue, and anemia scores, as well as the overall QOL scores (CLAS and FACT-An). These results indicate that corresponding with an increase in

Table 5
Proportion of correctors[a] (efficacy population)

Response	Epoetin alfa ($n=244$)	Placebo ($n=115$)	P value[b]
Corrector	165 (67.6%)	18 (15.7%)	<0.001
Non corrector	79 (32.4%)	97 (84.3%)	

[a] Patients who achieved hemoglobin ⩾12 g/dl unrelated to transfusions.
[b] Fisher exact test.

Table 6
Proportion of correctors[a] by sub group (efficacy population)

Sub group	Epoetin alfa ($n=244$)	Placebo ($n=115$)
Tumor type		
Solid	83/131 (63.4%)	10/61 (16.4%)
Hematologic	82/113 (72.6%)	8/54 (14.8%)
Hemoglobin stratum		
⩽10.5 g/dl	127/203 (62.6%)	14/100 (14.0%)
>10.5 g/dl	38/41 (92.7%)	4/15 (26.7%)

[a] Patients who achieved hemoglobin ⩾12 g/dl unrelated to transfusions.

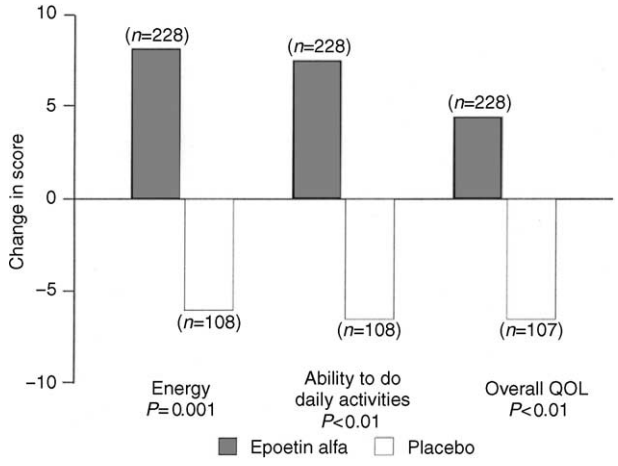

Fig. 4. Improved CLAS QOL scores by epoetin alfa versus placebo. The QOL CLAS scores from the beginning of the study to the last assessment were compared for epoetin alfa and placebo groups. The change in the patient's perceived energy level, ability to do daily activities, and overall QOL scores are shown for the epoetin alfa and placebo groups. Reprinted with permission [16].

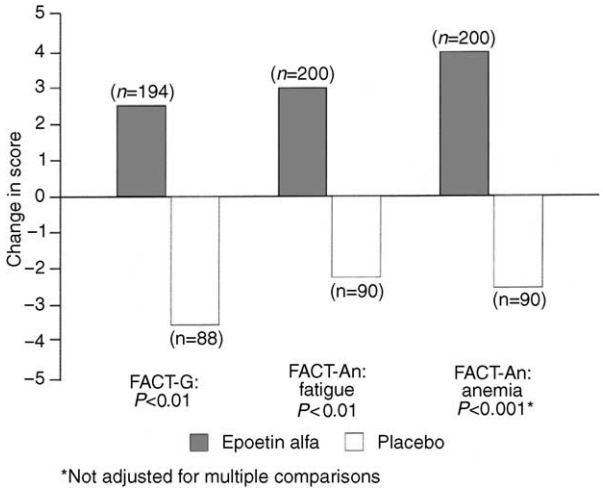

Fig. 5. Improved FACT-An QOL scores by epoetin alfa versus placebo. The QOL FACT-An scores from the beginning of the study to the last assessment were compared for epoetin alfa and placebo groups. The change in the patient's perceived fatigue, anemia, and overall (FACT-G) QOL scores are shown for the epoetin alfa and placebo groups. Reprinted with permission [16].

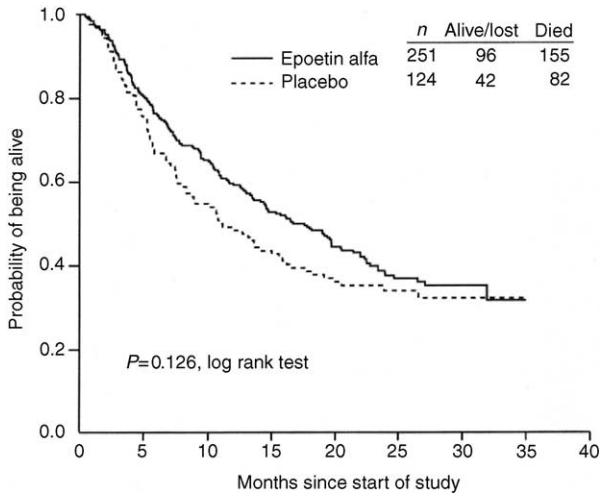

Fig. 6. Kaplan-Meier estimates of patient survival of epoetin alfa versus placebo. Kaplan–Meier probabilities were estimated for the epoetin alfa (—) and placebo (- - -) treatment groups over the course of the study. Adapted and reprinted with permission [16].

Hb levels and a decreased need for transfusion, epoetin alfa improved the QOL of these cancer patients.

Epoetin alfa was well tolerated. Adverse effect incidences have been separately reported [16] and were comparable between treatment groups (results not shown).

The survival results must be interpreted with caution because the study was not powered sufficiently to definitively assess survival, nor was it controlled for stage of disease, bone marrow involvement, intensity of chemotherapy, or disease progression. Nevertheless, the Kaplan–Meier 12-month survival estimates were 60% for epoetin alfa–treated patients and 49% for placebo-treated patients (Figs. 6 and 7). Median survival times were 17 months for epoetin alfa–treated patients and 11 months for placebo-treated patients. The log-rank test indicated a trend in overall survival for epoetin alfa ($P=0.13$).

Using the stepwise selection procedure of the Cox regression model, eight inclusion covariates were examined. Tumor type, age, baseline Hb level and neutrophil AUC were found to be significant. Including these

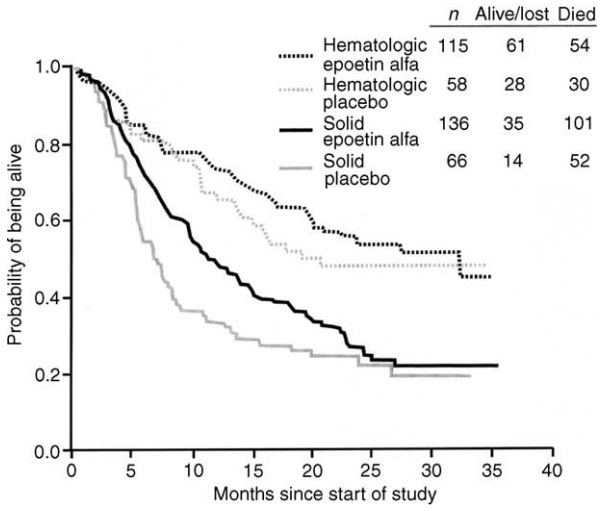

Fig. 7. Kaplan–Meier estimates of patient survival by tumor type. Kaplan–Meier probabilities were estimated for the solid (▬ and ▬) and hematologic (┅ and ┅) tumors for the epoetin alfa (┅ and ▬) and placebo (┅ and ▬) treatment groups over the course of the study. Tumor types are further classified in Table 2. Adapted and reprinted with permission [16].

covariates in the model, the estimated hazard ratio (placebo versus epoetin alfa) was 1.309 ($P = 0.052$), indicating that the risk of dying during the follow-up period was 31% higher for the patients receiving placebo.

4. Discussion

Many placebo-controlled and open-label clinical studies have demonstrated the safety and efficacy of epoetin alfa for the treatment of anemia in patients undergoing chemotherapy [13–16,19–23]. The results of these studies consistently indicated that epoetin alfa significantly increased Hb levels and decreased the need for blood transfusions. In the large-scale community-based studies, the increase in Hb levels was associated with improvements in the patient's energy level, their ability to do daily activities, and their overall QOL [13–15]. The results of Gabrilove *et al.* [15] utilized a once-weekly dosing regimen of epoetin alfa. In one study [14], there was a correlation between changes in Hb levels and changes in overall QOL that was independent of the response to chemotherapy.

The present study examined the administration of epoetin alfa to anemic cancer patients receiving non-platinum–based chemotherapy and its effect on the proportion of patients requiring transfusion, change in Hb levels and change in QOL scores. The placebo-controlled results confirm the effects seen in earlier studies. The proportion of patients requiring transfusions after the first 4 weeks of treatment was significantly smaller in the epoetin alfa group than in the placebo group ($P = 0.0057$) and the epoetin alfa–treated group had a significantly greater increase in Hb levels than did the placebo group ($P < 0.001$). Similar increases in Hb levels were seen for epoetin alfa–treated patients in the tumor and Hb strata. This increase in Hb levels for the epoetin alfa–treated patient also resulted in improvements in QOL that were not seen in placebo patients. Thus, these findings, which were obtained under randomized, placebo-controlled conditions, confirm and strengthen the validity of the previously described work [13–15,19–22].

In addition to the effect of epoetin alfa on transfusion requirements and Hb levels, the results of the present study demonstrated a significant and beneficial effect of epoetin alfa on QOL measures. The results showed significant ($P \leqslant 0.0048$) increases for epoetin alfa over placebo for five cancer- and anemia-specific primary QOL measures (FACT-G Total, FACT-An Fatigue subscale, CLAS: energy level, CLAS: ability to do daily activities, CLAS: overall QOL), and one secondary cancer- and anemia-specific QOL measure (FACT-An anemia subscale). It is important to note that these improvements in QOL were not seen in the placebo-treated patients. Again, these results, which were obtained under double-blind, placebo-controlled conditions and evaluated by rigorous statistical procedures, confirmed previously published studies that evaluated the effect of epoetin alfa on QOL [13–15,19–21].

In addition to the established relationship between Hb levels and QOL, there appears to be a possible relationship between Hb levels and patient survival. Analysis of the collected survival data in the present study revealed median survival times of 17 months with epoetin alfa and 11 months with placebo. Kaplan-Meier estimates showed a trend in survival favoring epoetin alfa ($P = 0.126$). When examined by tumor stratum, this trend continued for both solid and hematologic tumor groups and also compensated for the longer survival associated with hematologic malignancies. Further analysis with the Cox regression model controlling for potential prognostic factors (age, tumor stratum, baseline Hb level and AUC for neutrophils) confirmed the trend to increased survival overall. The meaning of the survival data is limited because the study was not controlled for variables that have an influence on survival, such as stage of disease, bone marrow involvement, intensity of chemotherapy and disease progression, and these data were not collected during the follow-up period. Thus, the longer survival of the epoetin alfa treatment group must be interpreted with caution. For the patient with advanced cancer, such an increase in survival time combined with a significant improvement in QOL would be important.

As in the present study which showed a trend in overall survival for cancer patients who received anemia treatment, a multivariate analysis of 191 patients who

received chemoradiotherapy and surgery for head and neck cancer found that higher Hb levels and use of epoetin alfa were independent prognostic factors for improved response to chemoradiotherapy and locoregional control ($P < 0.01$) [2]. Conversely, recent publications have questioned survival benefits with epoetin [24,25], although interpretation of these study results is complicated due to differences in study design (chemotherapy vs radiotherapy), population (non-anemic vs anemic) and post-trial analyses. These confounding results support the need for further investigation in this area. However, there are substantial data demonstrating the positive prognostic effect of non-anemic hemoglobin levels.

In a retrospective study that examined the importance of Hb levels during radiotherapy in 605 patients who had carcinoma of the cervix, results showed that average weekly nadir Hb (AWNH) level was correlated significantly with local control, disease-free survival and overall survival [26]. Furthermore, a review of 60 published papers reporting survival of cancer patients according to either Hb levels or presence of anemia found that anemia was associated with shorter survival times for patients with a variety of cancer types [27]. The relative increased risk of death in anemic patients ranged from 19% for lung carcinoma to 67% for lymphoma. The overall estimated increase in risk was 65%.

In summary, the results of the present study show that epoetin alfa is effective in significantly reducing the proportion of patients transfused, increasing Hb levels, and improving QOL in anemic cancer patients receiving non platinum–based chemotherapy. While the study was not designed or powered to evaluate survival, a trend in overall survival favoring patients treated with epoetin alfa was observed.

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Appendix. Participating investigators

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