Effects of Epoetin-α on Quality of Life of Cancer Patients with Solid Tumors Receiving Chemotherapy*

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Abstract. *Background: Erythropoietin corrects and prevents anemia and decreases the need for red blood cell (RBC) transfusions; its impact on quality of life (QOL) of cancer patients receiving chemotherapy is not clear. Patients and Methods: 399 patients with solid tumors and Hb level of ≤12 g/dl receiving chemotherapy were randomized to receive or not 10,000 IU epoetin-α thrice weekly. QOL was measured by the Functional Assessment of Cancer Therapy-Anemia (FACT-An) scale and various subscales at baseline, at two months and at the end of the study. Results: Changes in the average QOL scores were similar in the two groups. The improvement in Hb levels was significantly higher for the epoetin-α group, with a decrease in transfusion requirements compared to the control group. Conclusion: Epoetin-α does not improve QOL of patients with solid tumors receiving chemotherapy as assessed using FACT-An scale and various subscales, despite improving Hb levels and reducing transfusion requirements.*

The first study demonstrating that recombinant human erythropoietin can improve anemia associated with cancer was published 17 years ago (1). Since then many studies have confirmed that erythropoietin can increase hemoglobin (Hb) levels and reduce the need for red blood cell (RBC) transfusions in various groups of cancer patients (2).

Several non-randomized trials demonstrated that the benefits of erythropoietin extend to improvement in quality of life (QOL) (3-6). This was confirmed by a randomized double-blind placebo-control trial by Littlewood *et al*. (7). A subsequent trial by Witzig *et al*. indicated that this QOL benefit may be more modest than was initially believed (8). These two latest trials suggested a trend toward improved survival with the use of erythropoietin in cancer patients but they were not powered to detect survival differences. On the contrary, other studies produced inferior results concerning survival for patients receiving erythropoietin (9, 10).

The Hellenic Cooperative Oncology Group (HeCOG) published a prospective open-label randomized trial, which confirmed the efficacy of erythropoietin in preventing transfusions and significant anemia in patients with solid tumors receiving platinum-based chemotherapy (11). Assessment of the QOL was encouraged but was not a prerequisite for study entry. As a result only two centers assessed QOL rigorously. Based on data from this subgroup, no significant improvement in QOL was detected in cancer patients receiving erythropoietin.

HeCOG designed a randomized trial to directly address this important question. This trial, as reported here, assessed the effect of epoetin-α on QOL of cancer patients with solid tumors, receiving platinum or nonplatinum chemotherapy.

Patients and Methods

This was a multicenter prospective open-label randomized trial. The study was approved by the Protocol Review Committee of HeCOG and by the appropriate committees of the participating centers. Informed consent was received by patients prior to study entry. Inclusion criteria included histologically confirmed diagnosis of a

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solid tumor, age ≥18 years, Hb level of ≤12 g/dl, concurrent administration of chemotherapy (with anticipated minimum duration of 12 weeks), performance status of ≤2 according to the World Health Organization Scale, and life expectancy of at least 6 months. Patients with lymphomas or leukemia, uncontrolled hypertension, RBC transfusion during the previous two weeks, active bleeding or chronic illness associated with anemia (other than cancer) were excluded.

Patients receiving high-dose chemotherapy were not included. All patients received conventional doses; in particular, cisplatin was given at a dose of 60-100 mg/m^2 every 3-4 weeks and carboplatin at an area under the curve (AUC) 5-6 every 3-4 weeks.

Patients were randomized to receive either epoetin-α (Eprex; Janssen–Cilag, Buckinghamshire, UK) 10,000 IU thrice weekly subcutaneously or no treatment. If the Hb increased to more than 14 g/dl, epoetin-α was discontinued until the Hb was less than 12 g/dl and then restarted at a dose of 10,000 IU twice weekly.

An oral daily dose of 200 mg of elemental iron was recommended to all participating patients; in order to maintain appropriate iron availability and iron stores. Adaptive blocked stratified randomization balanced by center was performed centrally at the HeCOG data office with stratification factor as the type of chemotherapy (platinum or nonplatinum; patients receiving oxaliplatin were allocated to the nonplatinum group). The primary end point was to assess the effect of epoetin-α on the QOL of cancer patients receiving chemotherapy, with secondary end points being the assessment of the effect of epoetin-α on RBC transfusion needs and anemia.

QOL was evaluated at baseline, at two months and at the end of the study using the Functional Assessment of Cancer Therapy-Anemia (FACT-An) scale (12). The FACT-An instrument is a 55-item questionnaire assessing the five major domains of QOL and also providing some disease-specific information on cancer patients with anemia. The FACT-General (FACT-G) subscale uses 27 items from the FACT-An instrument and was also evaluated. It consists of 4 subscales: physical well-being (PWB), social/family well-being (SFWB), emotional well-being (EWB) and functional well-being (FWB). The FACT-An instrument includes two more subscales, also evaluated in our study, relating to fatigue: the fatigue subscale (FATS) and the non fatigue subscale (NFATS). Total anemia subscale score (ANS) is the sum of FATS and NFATS. FACT-An total score is the sum of PWB, SFWB, EWB, FWB and ANS. FACT fatigue total score (TOTFAT) is the sum of PWB, SFWB, EWB, FWB and FATS. Finally, trial outcome index (TOI) is the sum of PWB, FWB and ANS. Full blood count, sodium, potassium, calcium, creatinine, bilirubin, transaminases and alkaline phosphatase were assessed every 3 or 4 weeks, depending on the chemotherapy schedule. Transfusion of RBCs was permitted during the study, at the discretion of the physician, but was to be avoided in patients with an Hb level greater than 8.5 g/dl, unless clinically indicated. Upon completion of chemotherapy, response was assessed according to WHO classification criteria.

Statistical analysis. Patient and tumor characteristics as well as outcome measures such as response, number of transfusions and transfusion units were compared between treatment groups by Fisher's exact test or Wilcoxon rank sum test.

Information on transfusions are reported for the first 6 cycles of treatment. Mixed effect models were used to explore the effect of treatment on the time progression of QOL measures and Hb level (13). The models of the change from baseline with intercept as a random effect, controlling for the stratification factor of chemotherapy treatment (platinum *vs*. nonplatinum) and baseline value, included treatment group (epoetin-α *vs*. control), time and the respective interactions as covariates. FACT-An total score was the primary QOL measure, while analysis was also performed for each of the subscale scores (PWB, SFWB, EWB, FWB, FATS, NFATS) and partial sums (FACT-G, ANS, TOTFAT, TOI). Other covariates of interest included in the models were baseline Hb level (Hb≤10.5 g/dl *vs*. Hb>10.5 g/dl).

The study was designed for a power of 80% within each platinum treatment category, for a two-sided test at a=0.05 to detect a difference in mean standardized change (Delta) of a relatively small magnitude of 0.30 in the primary measure, assuming a correlation of 0.80 between observations at different time points (176x0.26=46 patients per arm) (14, 15).

Best response to treatment is reported excluding these patients who received adjuvant treatment or had non measurable or non evaluable disease. Survival (S) was estimated from randomisation date to the date of last follow-up or until the patient's death. Time to disease progression (TTP) was deemed as the time between randomization and progression documented clinically and/or radiologically. Patients who died from the disease without having documented progression were considered as events at the estimate of TTP. All tests were two-sided and performed at significance level a=0.05. Nominal *p*-values are reported without adjustment for multiple comparisons. The SAS statistical package was used for the analysis (SAS Institute Inc., Cary, USA).

Results

Between November 1999 and October 2001, 399 patients with various solid tumors were randomized to the study. Data from 337 patients were available for the analysis. Eighteen patients had not completed the QOL questionnaire, 5 patients were randomized with hemoglobin levels over 12 g/dl and one patient had a PS 3. One center did not provide patients' follow-up information; the 27 patients of this center are excluded from the analysis. Hematological data were missing for 11 patients with available QOL data. From the 337 patients, 167 were randomized in the epoetin-α group and 170 in the control group. No significant differences between treatment groups were found for the patient and tumor characteristics presented in Table I.

Quality of Life. Mean scores across time for FACT-G, FATS, NFATS ANS, FACT-An Total, TOTFAT and TOI scores are presented in Table II and Figure 1 (a-d). Patients with only two measurements had the last (second) measurement up to 4.3 months after baseline, while patients with three measurements had their last measurement up to 6.2 months after baseline. Based on the mixed effects models analysis, from the four subscales of FACT-G (PWB, SFWB, EWB and FWB), only the mean change in FWB was found to differ significantly across time between the epoetin-α and control groups regardless of whether the treatment included a platinum or nonplatinum regimen (p=0.024). This result is not significant when adjusting for multiple comparisons. Mean changes in all other FACT-An scale scores were found

Table I. *Basic patient and tumor characteristics*.

	EPO-A (N=167)	Control (N=170)
Age (years)		
Median	61	63
Range	22-82	30-89
	N (%)	N (%)
PS		
0	62 (37)	71 (42)
1	81 (49)	84 (50)
2	24 (14)	15 (8)
Gender		
Male	88 (53)	81 (48)
Female	79 (47)	89 (52)
Primary site of malignancy		
Genitourinary	19 (11)	25 (15)
Gastrointestinal	45 (27)	52 (31)
Gynecologic	30 (18)	31 (18)
Breast	26 (16)	27 (16)
Lung	33 (20)	19 (11)
Head and neck	5 (3)	6 (3.5)
Unknown primary	8(5)	5 (3)
Other	1 (1)	5 (3)
History of transfusion (s)		
No	141 (84)	133 (78)
Yes	20 (12)	22 (13)
Unknown	6 (4)	15 (9)
Platinum based chemotherapy		
No	102 (61)	108 (63.5)
Yes	65 (39)	62 (36.5)
Baseline hemoglobin (g/dL)		
Mean (±SD)	10.15 (±0.69)	10.30 (±0.58)
Baseline hematocrit (%)		
Mean (±SD)	32.2 (±4.84)	32.6 (±2.78)

EPO-A: Epoetin-α, PS: performance status, SD: standard deviation.

to be insignificant. Baseline Hb level did not affect these results, whether using the actual baseline Hb value in the models, or looking at differences by category of Hb (<10.5 g/dl *vs*. >10.5 g/dl). We evaluated changes in QOL in Hb responders, defined as an improvement of at least 1 g/dl within 6 to 8 weeks of epoetin-α administration, excluding transfused patients, and compared these results with those of non-responders. No differential effect of epoetin-α on QOL was detected between these two groups.

Transfusion requirements. Sixteen patients in the epoetin-α group (10%) and 36 patients in the control group (21%) were transfused during treatment (p=0.0035). One thousand two hundred and sixteen cycles of treatment were given (590 in the epoetin-α group and 626 in the control group). Transfusion was needed in 51 cycles (8%) in the control group *vs*. 19 cycles (3%) in the epoetin-α group (p<0.001). The mean number of transfusion units needed per patient was 0.24 and 0.61 for the epoetin-α group and the control group, respectively (p=0.003). Among transfused patients, the maximum needed transfusion units was similar in the two groups (median=2).

Baseline Hb levels were 10.15 (±0.69) g/dl for the epoetin-α group and 10.28 (±0.58) g/dl for the control group. Mean Hb levels (g/dl) after each cycle of treatment for epoetin-α and control group, separately for platinum and nonplatinum regimens are shown in Figure 2. A mean increase of 5.12 (intercept, p<0.0001) was estimated for Hb levels according to the model. Mean changes from baseline for Hb levels differed significantly across time between the epoetin-α and control groups (p=0.0005), adjusting for the corresponding baseline value (p<0.0001) and whether the treatment included a platinum or nonplatinum regimen. The improvement in mean Hb levels was significantly higher in patients treated with a nonplatinum regimen compared to those treated with platinum (mean increase difference of 0.63 g/dl, p<0.0001), as well as in patients in the epoetin-α group (mean increase difference of 1.08 g/dl, p=0.002).

Disease outcome. Patients who received adjuvant treatment and those with nonmeasurable disease (n=69) were excluded from response assessment. The two groups did not differ significantly in terms of overall response rate (ORR) (26% *vs*. 22% p=0.57). The median follow-up period was 14.3 months.

Median TTP was 6.82 (0.07-61.67+) months for the epoetin-α group and 7.25 (0.03-59.61+) months for the control group. No significant differences were observed in terms of TTP between the two treatment groups (log rank: p=0.86, Breslow: p=0.94, Tarone –Ware: p=0.99); this was also true with or without adjustment for platinum/non-platinum chemotherapy (log rank: p=0.88, Breslow: p=0.84, Tarone – Ware: p=0.95) (Figure 3).

Median overall survival was 10.39 (0.07-61.67+) months for the epoetin-α group and 14.59 (0.03-59.61+) months for the control group. Patients treated with epoetin-α did not have significantly worse overall survival based on the log-rank test but they did when looking at tests that place more weight on events happening in earlier time points (log-rank: p=0.16, Breslow: p=0.02, Tarone-Ware: p=0.04). This result remains after adjustment has been made for platinum/non-platinum chemotherapy (log-rank: p=0.16, Breslow: p=0.03, Tarone-Ware: p=0.04) (Figure 4).

Discussion

Recombinant human erythropoietin has been shown in clinical trials to correct or prevent anemia and to reduce the need for RBC transfusion (1-8). Several large trials have demonstrated that the benefits of recombinant human erythropoietin extend to improvement in QOL of cancer patients receiving platinum and nonplatinum chemotherapy (3, 4, 7).

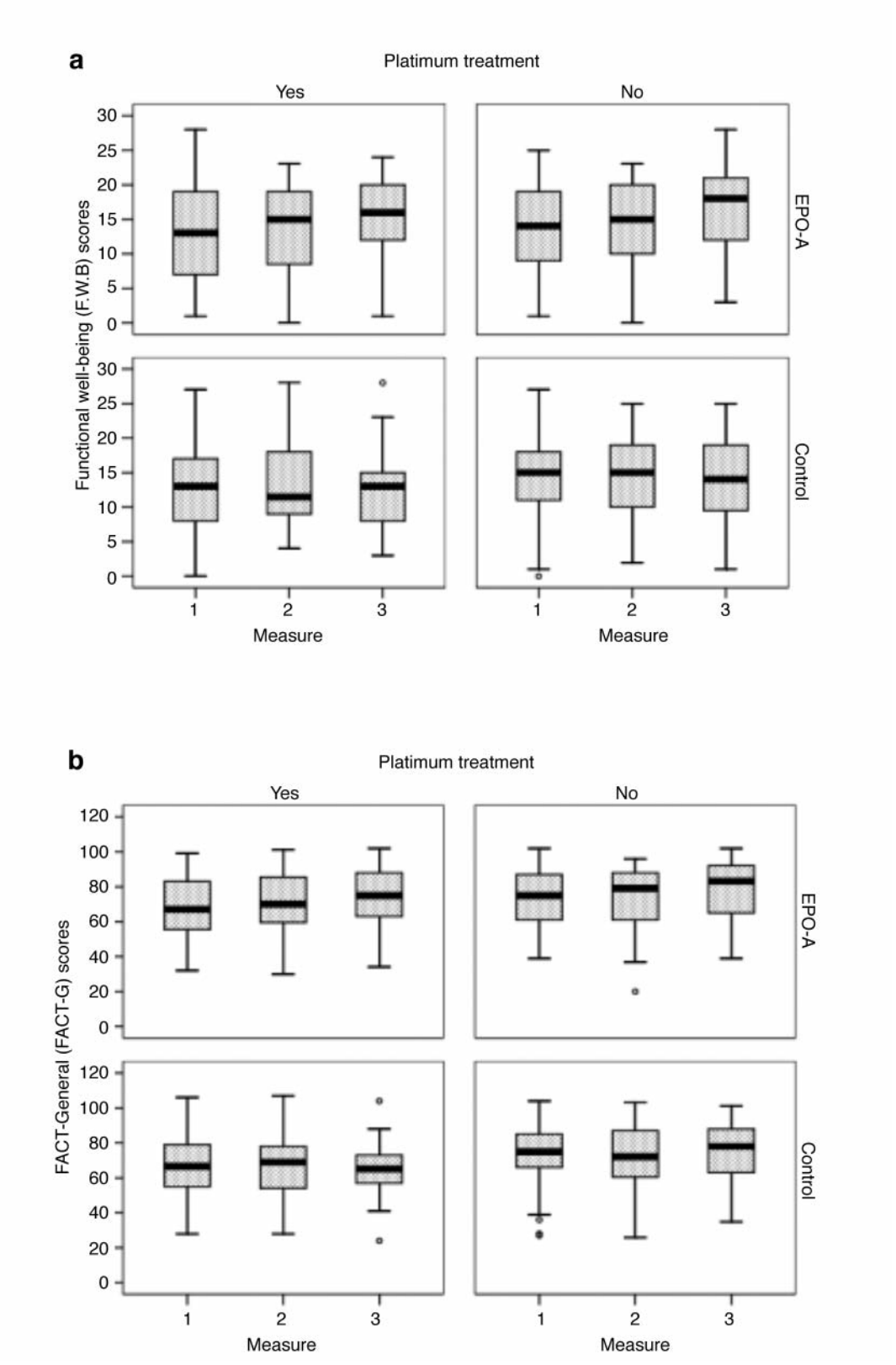

Figure 1. *continued*

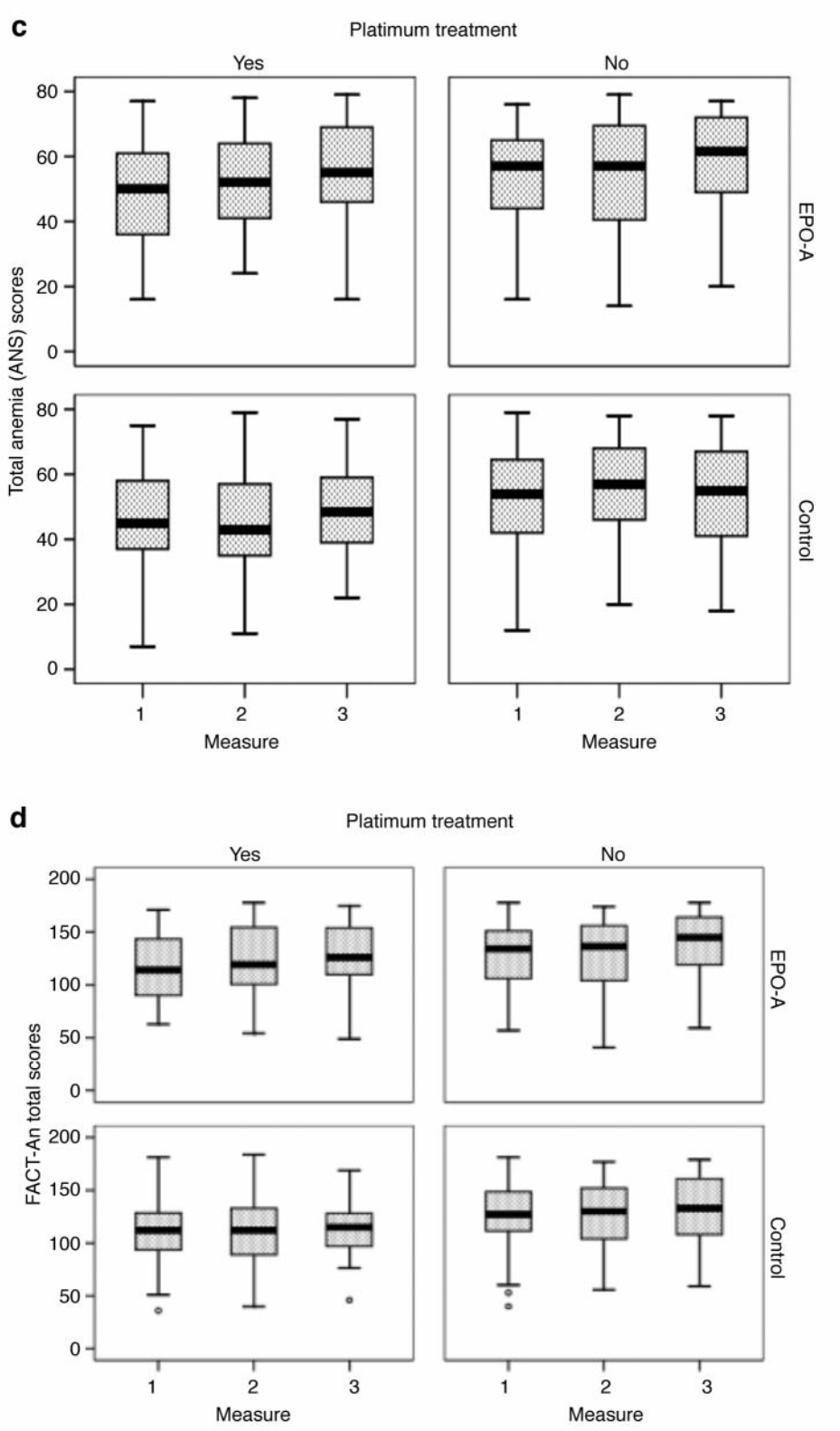

Figure 1. *a) Functional well-being (FWB), b) FACT-General (FACT-G), c) Total anemia (ANS) and d) FACT-An total scores at baseline (1), at two months (2) and at the end of the study (3).*

Table II. *Mean (±SD) Fact-An scores at baseline (1), two months (2) and at the end of the study (3).*

	Nonplatinum-based chemotherapy			Platinum-based chemotherapy		
	1 (N=214)	2 (N=168)	3 (N=102)	1 (N=132)	2 (N=92)	3 (N=53)
PWB						
EPO-A	20.14 (±5.25)	20.38 (±5.80)	20.80 (±5.59)	17.48 (±6.14)	19.83 (±5.37)	19.88 (±5.39)
Control	20.06 (±5.43) (N=191)	20.00 (±5.90) (N=150)	19.46 (±6.80) (N=87)	17.46 (±6.29) (N=107)	17.16 (±7.11) (N=77)	17.63 (±6.49) (N=44)
SFWB						
EPO-A	21.68 (±4.0)	21.15 (±4.58)	22.19 (±3.99)	21.62 (±4.50)	20.27 (±5.07)	21.23 (±5.26)
Control	21.17 (±4.59) (N=205)	21.05 (±4.05) (N=164)	21.49 (±3.36) (N=99)	21.48 (±5.15) (N=126)	20.68 (±4.39) (N=92)	19.91 (±5.44) (N=52)
EWB						
EPO-A	17.18 (±5.26)	18.09 (±5.62)	18.63 (±5.17)	15.95 (±5.05)	16.40 (±5.66)	17.61 (±5.46)
Control	17.19 (±5.66) (N=214)	17.97 (±5.45) (N=167)	17.38 (±5.52) (N=101)	15.19 (±5.64) (N=128)	15.84 (±6.0) (N=92)	16.15 (±4.89) (N=52)
FWB						
EPO-A	13.48 (±5.80)	14.41 (±6.19)	15.85 (±6.35)	12.97 (±6.48)	13.86 (±5.96)	15.46 (±5.38)
Control	14.62 (±5.88) (N=182)	14.59 (±5.51) (N=147)	14.0 (±6.19) (N=85)	12.47 (±6.0) (N=103)	12.86 (±5.95) (N=72)	12.69 (±5.96) (N=44)
FACT-G						
EPO-A	73.24 (±15.95)	73.55 (±17.61)	78.06 (±17.38)	67.92 (±17.0)	70.26 (±17.51)	72.64 (±17.69)
Control	74.16 (±16.70) (N=215)	73.07 (±16.57) (N=166)	75.0 (±16.4) (N=102)	66.06 (±17.19) (N=130)	66.09 (±18.64) (N=93)	66.18 (±17.16) (N=51)
FATS						
EPO-A	32.63 (±11.66)	32.27 (±13.46)	36.17 (±12.38)	29.12 (±12.03)	32.09 (±11.16)	33.68 (±11.86)
Control	31.95 (±11.89) (N=215)	33.40 (±11.82) (N=166)	31.69 (±14.14) (N=102)	27.49 (±12.15) (N=130)	26.82 (±13.27) (N=93)	30.19 (±11.07) (N=50)
NFATS						
EPO-A	20.87 (±3.61)	20.74 (±4.63)	21.90 (±4.06)	19.74 (±4.19)	20.23 (±4.18)	20.79 (±5.27)
Control	20.52 (±4.57) (N=215)	21.69 (±3.81) (N=166)	20.92 (±3.98) (N=102)	19.08 (±4.44) (N=130)	19.10 (±4.38) (N=93)	19.50 (±3.47) (N=51)
ANS						
EPO-A	53.5 (±14.51)	53.01 (±17.14)	58.07 (±15.57)	48.86 (±14.85)	52.30 (±14.83)	53.64 (±16.78)
Control	52.48 (±15.59) (N=183)	55.10 (±14.60) (N=145)	52.61 (±17.35) (N=85)	46.54 (±15.24) (N=103)	45.90 (±17.02) (N=73)	49.69 (±13.92) (N=41)
FACT-An TOTAL SCORE						
EPO-A	127.18 (±28.73)	126.64 (±32.99)	136.92 (±31.37)	116.08 (±29.94)	121.61 (±30.74)	126.40 (±34.19)
Control	127.46 (±29.53) (N=183)	128.19 (±29.24) (N=145)	129.57 (±31.02) (N=85)	110.81 (±29.02) (N=103)	111.14 (±32.95) (N=73)	113.14 (±28.18) (N=42)
TOTFAT						
EPO-A	106.47 (±25.97)	106.06 (±29.47)	114.92 (±28.39)	96.39 (±27.58)	101.16 (±27.21)	106.29 (±28.60)
Control	106.85 (±26.17) (N=213)	106.63 (±26.39) (N=165)	108.28 (±28.17) (N=101)	92.0 (±26.50) (N=126)	92.26 (±29.60) (N=89)	93.95 (±25.43) (N=50)
TOI						
EPO-A	87.22 (±23.62)	88.14 (±27.02)	94.61 (±26.17)	79.61 (±25.04)	86.39 (±24.71)	89.60 (±25.52)
Control	87.34 (±24.49)	89.84 (±24.0)	86.75 (±28.04)	76.11 (±24.37)	76.25 (±28.80)	78.84 (±24.45)

EPO-A: Epoetin-α, SD: standard deviation, PWB: physical well-being, SFWB: social/family well-being, EWB: emotional well-being, FWB: functional well-being, FACT-G: functional assessment of cancer therapy-general, FATS: fatigue subscale, NFATS: non-fatigue subscale, ANS: anemia subscale score, FACT: functional assessment of cancer therapy-anemia, TOTFAT: fatigue total score, TOI sum of PWB, FWB, ANS.

This was not in agreement with the findings of a study published recently from our group (11). In that randomized open-label study, the main endpoint was to assess the efficacy of erythropoietin in preventing transfusions and significant anemia in patients with solid tumors receiving platinum-based chemotherapy. Assessment of the QOL was encouraged but was not an objective of the study. Fifty-nine out of 144 patients had both baseline and termination QOL assessment.

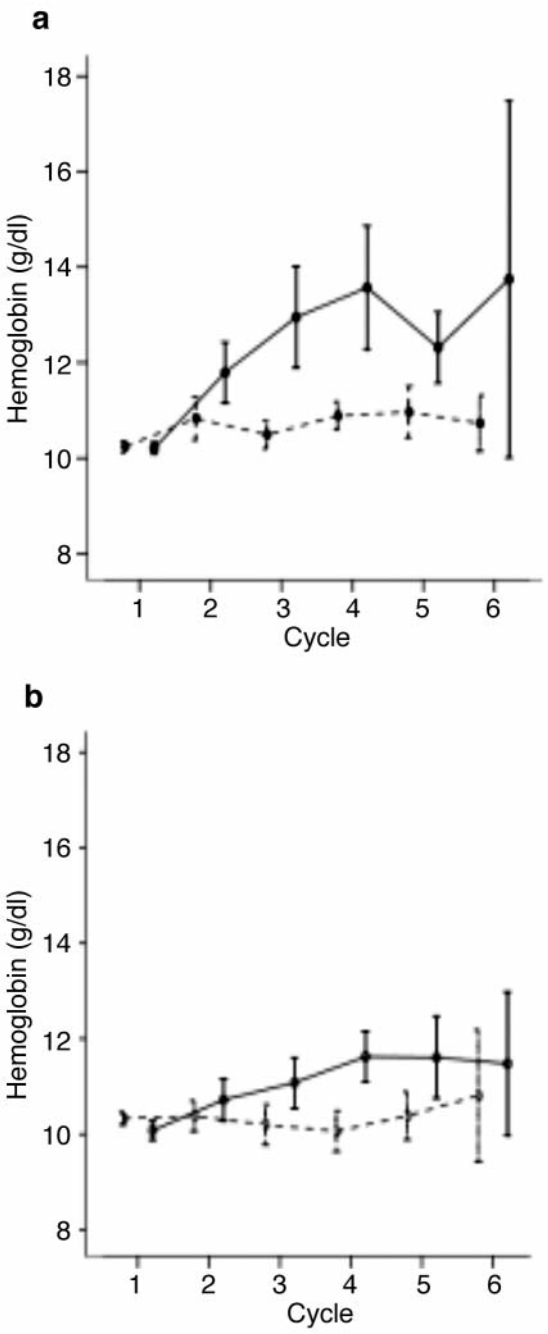

Figure 2. *Changes in Hb levels over time for epoetin-α (_____) and the control (- - - -) group in nonplatinum- (a) and platinum-treated (b) patients. Values are means ±95% confidence interval.*

An improvement in confinement to bed, which is part of the physical functioning scale, and in the global health status was only observed in patients receiving epoetin-α, but no significant differences between epoetin-α and control groups were found.

The present study had as primary endpoint the assessment of the efficacy of epoetin-α on QOL of cancer patients receiving chemotherapy. QOL was assessed at baseline, at two months and at the end of the study using the FACT-An scale. No significant differences were found between the epoetin-α and the control group for the various subscales of FACT-An *e.g.* FACT-G, FATS, NFATS, ANS. Only the FWB subscale was significantly better between the two groups across time, a finding that can be attributed to the limitations of multiple testing.

There are several potential reasons for this lack of effect. First, RBC transfusions were permitted at the physician's discretion and therefore the increased transfusion rate in the patients of the control arm have masked the true difference in QOL effects between the two arms. Second, the QOL of the cancer patient is determined by various factors such as Hb level, type of cancer, type of treatment, type of metastases, level of pain and psychological state of the patient and epoetin corrects only one of these. Third, a mixed population of cancer patients was included in our study: patients with various tumors and stages of disease, receiving adjuvant chemotherapy or chemotherapy for metastatic disease, heavily pretreated and chemo-naive patients. In particular, the inclusion of both patients on adjuvant and these on palliative cancer treatment is a conceptual problem when QOL is studied. Finally, patients with an Hb level close to 12 g/dl may enjoy relatively good QOL making it impossible to improve QOL. The selection of Hb ≤12 g/dl as the cut-off level for starting treatment with erythropoietin is no longer acceptable, but at the time our study was conducted, this was common practice.

Several nonrandomized trials demonstrated that erythropoietin positively affects QOL (3-6). However, a systematic review of the effectiveness of erythropoietin with regard to QOL questioned the validity and reliability of the data reported in the literature (16). One major limitation described is the lack of masked testing of patients. Other pitfalls included lack of definition of QOL and adequate power calculations, as well as incomplete reports on methods for handling missing data. These findings have been supported by two systematic reviews (2, 17). There are three large randomized studies in the literature with the QOL assessment in patients receiving human recombinant erythropoietin as endpoint (7, 8, 18). In the first study by Littlewood *et al*., QOL assessment was a secondary endpoint (7). QOL was measured using FACT-An and the Cancer Linear Analog Scale (CLAS, also known as LASA). Significant differences for epoetin-α over placebo were found for all cancer- and anemia-specific QOL measures that were reported (FACT-G, FATS, Anemia Subscale of FACT-An, CLAS, overall QOL). In the second randomized trial by Witzig *et al*., QOL assessment was a primary endpoint, as it was in our study (8). The QOL instruments used in that study were the Unicscale, the anemia subscale of the FATS,

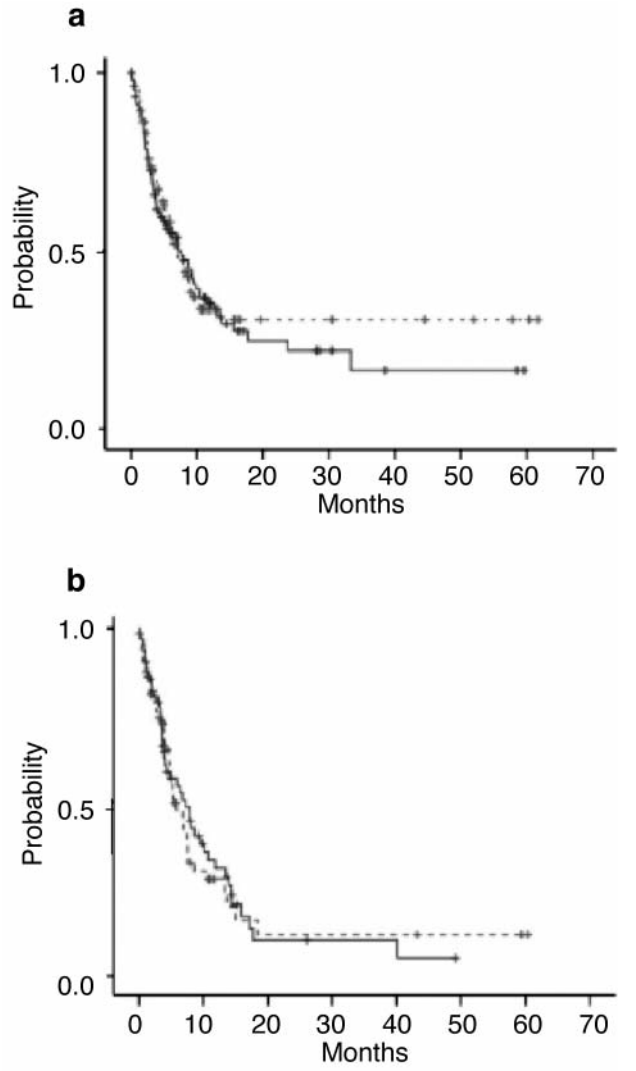

Figure 3. *Time to progression (TTP) for EPO-A (- - - -) and the control (_____) group (p=0.88) in non platinum - (a) and platinum - (b) treated patients.*

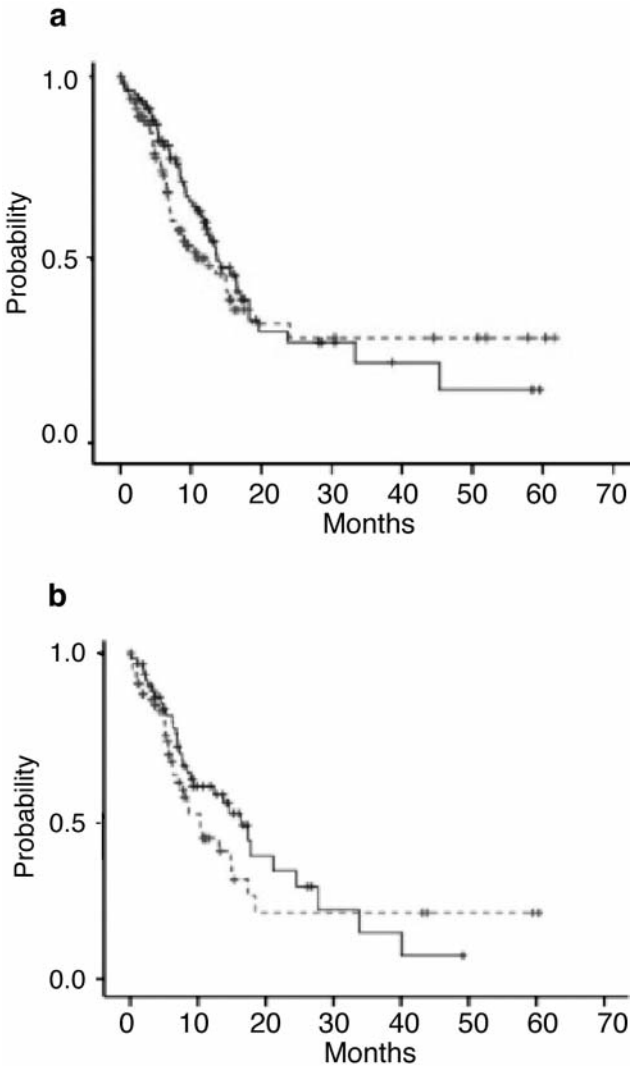

Figure 4. *Survival for EPO-A (- - - -) and the control (_____) group (p=0.16) in non platinum - (a) and platinum - (b) treated patients.*

the general subscale of FACT-An and a symptom distress scale (SDS). Patients treated with epoetin-α had some improvement in the QOL score, measured with the above scales and subscales, but these differences did not reach statistical significance. Therefore our findings are in accordance with these.

Finally, Wright and colleagues recently published a multicenter randomized, double-blind placebo-controlled trial to evaluate the impact of epoetin-α on the primary endpoint of QOL in patients with non-small cell lung cancer and disease-related anemia (18). Patients receiving high-dose thoracic radiation or platinum-based chemotherapy were excluded, with the intent to focus on patients whose anemia was not related to systemic treatment. The planned sample size was 300 patients. Due to reports of thrombotic events in other epoetin trials, an unplanned safety analysis after the first 70 patients revealed a significant difference in the median survival in favor of the group of patients in the control group. The steering committee decided to close the study. No significant differences were seen in terms of QOL endpoints, which were complicated by the small sample size and a baseline imbalance in FACT-An score.

Not surprisingly, we found that transfusion requirements were significantly reduced in the epoetin-α group of our study, which is consistent with all the previous trials. Only 10% of patients were transfused in the epoetin-α group as compared to 21% of patients in the control group, while the mean number of transfusion units needed was

significantly higher in the control group (0.24 *vs*. 0.61, p=0.003). The improvement of hemoglobin levels (g/dl) was significantly higher for the epoetin-α group. These findings are consistent with the results seen in two large open-label nonrandomized studies enrolling over 4,000 cancer patients with various tumor types under chemotherapy (3, 4). Both studies tested the same dose and schedule of epoetin-α, namely 10,000 IU three times per week, subcutaneously. Both studies showed a rise in the average Hb level of ~2 g/dl resulting in a reduction in the number of transfusions of 50% and 80% respectively. These results have also been confirmed in a randomized study by Littlewood *et al*. (7). Compared with patients receiving placebo, transfusion needs in the epoetin-α group were significantly reduced (25% *vs*. 40%).

Since low serum ferritin levels and low transferin saturation before the start of epoetin-α treatment might impair efficacy, we gave oral iron to all patients included in our study, according to the clinical practice at the time trial was initiated. Owing to the elevation in iron metabolism of cancer patients, the prophylactic application of iron might have had a positive effect in both groups of patients.

Concerning disease outcome, no difference was detected in ORR or TTP, while the median overall survival was 10.39 months in the epoetin-α group and 14.59 months in the control group. Based on the log-rank test, no significant effect of epoetin-α on survival was found. Of note, using other tests with more weight on events happening the earlier time period, the overall survival of patients receiving epoetin-α was significantly worse as compared to that of the control group. This result should be viewed with skepticism, as survival was not the primary endpoint of this study using a heterogeneous population of patients *i.e*., patients with various solid tumors, receiving chemotherapy in the adjuvant or metastatic setting were included. Nevertheless, six other studies have produced inferior results concerning survival and/or progression-free survival for the group receiving human recombinant erythropoietin [BEST, ENHANCE, 20010103, 20000061, EPO-CAN-20, DAHANSA (9, 10, 18-21)]. Four of these studies – BEST, ENHANCE, EPO-CAN-20 and DAHANSA – have been published in peer reviewed journals while the other two are not available as full reports but data are available in ODAC briefing documents posted on the US Food and Drug Administration Website. Clinical outcomes might represent a balance between effects of erythropoietin on anemia, adverse effects of the drug (*e.g*. thromboembolism), direct effects of erythropoietin on tumor cells (*e.g*. oxygenation, tumor growth due to erythropoietin receptors on diverse tumor cells). Some of these effects could promote tumor growth and others could inhibit it. Dr Henke and colleagues explored the possible relationship between erythropoietin receptors in patients with head and neck cancer and their poor survival and concluded that erythropoietin might adversely affect prognosis if cancer cells express erythropoietin receptors (22). The complex biology of the signaling process, the variation in *in vitro* models, as well as the importance of determining not only the presence but the function of epo-receptors, will be a critical part of ongoing preclinical and clinical investigation.

Finally, we would like to report that pure red cell aplasia (PRCA), a rare complication of epoetin-α found in patients with chronic renal failure (23), was not observed in any patients in this study.

In conclusion, our study did not detect significant QOL benefit in patients receiving epoetin-α, while it confirmed that transfusion requirements are reduced and Hb levels are increased with epoetin-α.

References

1 Ludwig H, Fritz E, Kotzmann H, Hocker P, Gisslinger H and Barnas U: Erythropoietin treatment of anemia associated with multiple myeloma. N Engl J Med *322*: 1693-1699, 1990.

2 Seidenfeld J, Piper M, Flamm C, Hasselblad V, Armitage JO, Bennett CL, Gordon MS, Lichtin AE, Wade JL 3rd, Woolf S and Aronson N: Epoetin treatment of anemia associated with cancer therapy: a systematic review and meta-analysis of controlled clinical trials. J Natl Cancer Inst *93*: 1204-1214, 2001.

3 Glaspy J, Bukowski R, Steinberg D, Taylor C, Tchekmedyian S and Vadhan-Raj, S, for the Procrit Study Group: Impact of therapy with epoetin alfa on clinical outcomes in patients with nonmyeloid malignancies during cancer chemotherapy in community oncology practice. J Clin Oncol *15*: 1218-1234, 1997.

4 Demetri GD, Kris M, Wade J, Degos L and Cella D: Quality-of-life benefit in chemotherapy patients treated with epoetin alfa is independent of disease response or tumor type: results from a prospective community oncology study, for the Procrit Study Group. J Clin Oncol *16*: 3412-3425, 1998.

5 Gabrilove JL, Cleeland CS, Livingston RB, Sarokhan B, Winer E and Einhorn LH: Clinical evaluation of once-weekly dosing of epoetin alfa in chemotherapy patients: improvements in hemoglobin and quality of life are similar to three-times-weekly dosing. J Clin Oncol *19*: 2875-2882, 2001.

6 Desai J and Demetri GD: Recombinant human erythropoietin in cancer-related anemia: an evidence-based review. Best Pract Res Clin Haematol *18*: 389-406, 2005.

7 Littlewood TJ, Bajetta E, Nortier JW, Vercammen E and Rapoport B: Effects of epoetin alfa on hematologic parameters and quality of life in cancer patients receiving nonplatinum chemotherapy: results of a randomized, double-blind, placebo-controlled trial. J Clin Oncol *19*: 2865-2874, 2001

8 Witzig TE, Silberstein PT, Loprinzi CL, Sloan JA, Novotny PJ, Mailliard JA, Rowland KM, Alberts SR, Krook JE, Levitt R and Morton RF: Phase III, randomized, double-blind study of epoetin alfa compared with placebo in anemic patients receiving chemotherapy. J Clin Oncol *23*: 2606-2617, 2005.

9 Henke M, Laszig R, Rube C, Schafer U, Haase KD, Schilcher B, Mose S, Beer KT, Burger U, Dougherty C and Frommhold H: Erythropoietin to treat head and neck cancer patients with anaemia undergoing radiotherapy: randomised, double-blind, placebo-controlled trial. Lancet *362*: 1255-1260, 2003.

10 Leyland-Jones B, Semiglazov V, Pawlicki M, Pienkowski T, Tjulandin S, Manikhas G, Makhson A, Roth A, Dodwell D, Baselga J, Biakhov M, Valuckas K, Voznyi E, Liu X and Vercammen E: Maintaining normal hemoglobin levels with epoetin alfa in mainly nonanemic patients with metastatic breast cancer receiving first-line chemotherapy: a survival study. J Clin Oncol *23*: 5960-5972, 2005.

11 Bamias A, Aravantinos G, Kalofonos C, Timotheadou N, Siafaka V, Vlahou I, Janinis D, Pectasides D, Pavlidis N and Fountzilas G: Prevention of anemia in patients with solid tumors receiving platinum-based chemotherapy by recombinant human erythropoietin (rHuEpo): a prospective, open label, randomized trial by the Hellenic Cooperative Oncology Group. Oncology *64*: 102-110, 2003.

12 Cella D: The Functional Assessment of Cancer Therapy-Anemia (FACT-An) Scale: a new tool for the assessment of outcomes in cancer anemia and fatigue. Semin Hematol *34*: 13-19, 1997.

13 Laird NM and Ware JH: Random-effects models for longitudinal data. Biometrics *38*: 963-974, 1982.

14 Machin D, Campbell MJ, Fayers PM and Pinol APY: Sample Size Tables for Clinical Studies, 2nd Edition. Oxford, Blackwell Science, 1997.

15 Cohen J: Statistical Power Analysis for the Behavioural Sciences, 2nd Edition. New Jersey, Lawrence Earlbaum, 1998.

16 Bottomley A, Thomas,R, van Steen K, Flechtner H and Djulbegovic B: Human recombinant erythropoietin and quality of life: a wonder drug or something to wonder about? Lancet Oncol *3*: 145-153, 2002.

17 Bohlius J, Langensiepen S, Schawarzer G, Seidenfeld J, Piper M, Bennet C and Engert A: Erythropoietin for patients with malignant disease, CD003407 ed, Cochrane Database Syst Rev 3, 2004.

18 Wright JR, Ung YC, Julian JA, Pritchard KI, Whelan TJ, Smith C, Szechtman B, Roa W, Mulroy L, Rudinskas L, Gagnon B, Okawara GS and Levine MN: Randomized, double-blind, placebo-controlled trial of erythropoietin in non-small-cell lung cancer with disease-related anemia. J Clin Oncol *25*: 1027-1032, 2007.

19 Food and Drug Administartion Oncologic Drugs Advisory Committee Briefing Document. Continuing Reassessment of the Risks of Erythropoiesis-stimulating Agents (ESAS) Administered for the Treatment of Anemia Associated with Cancer Chemotherapy: Washington, DC: US Food and Drug Administration http://www.fda.gov/ohrms/dockets/ac/07/briefing/ 2007-4301b2-02-FDA.pdf, 2007.

20 Danish Head and Neck Cancer Group (DAHANCA): Study of the importance of novel erythropoiesis-stimulating protein (Aranesp) for the effect of radiotherapy in patients with primary squamous cell carcinoma of the head and neck. Aarhus, Denmark: Aarhus University Hospital, 2007. http://www.dahanca.dk/get_media_file.php?mediaid=125

21 Hedenus M, Adriansson M, San Miguel J, Kramer MH, Schipperus MR, Juvonen E, Taylor K, Belch A, Altes A, Martinelli G, Watson D, Matcham J, Rossi G and Littlewood TJ, Darbepoetin Alfa 20000161 Study Group: Efficacy and safety of darbepoetin alfa in anaemic patients with lymphoproliferative malignancies: A randomized, double-blind, placebo-controlled study. Br J Haematol *122*: 394-403, 2003.

22 Henke M, Mattern D, Pepe M, Bezay C, Weissenberger C, Werner M and Pajonk F: Do erythropoietin receptors on cancer cells explain unexpected clinical findings? J Clin Oncol *24*: 4708-4713, 2006

23 Casadevall N, Nataf J, Viron B, Kolta A, Kiladjian JJ, Martin-Dupont P, Michaud P, Papo T, Ugo V, Teyssandier I, Varet B and Mayeux P: Pure red-cell aplasia and antierythropoietin antibodies in patients treated with recombinant erythropoietin. N Engl J Med *346*: 469-475, 2002.

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