# Quality-of-Life and Health Benefits of Early Treatment of Mild Anemia

## *A Randomized Trial of Epoetin alfa in Patients Receiving Chemotherapy for Hematologic Malignancies*

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**BACKGROUND.** Chemotherapy-related anemia is prevalent among patients with hematologic malignancies. A randomized, open-label, multicenter trial of early versus late epoetin alfa in this population was conducted, focusing on quality of life (QOL).

**METHODS.** Patients with non-Hodgkin lymphoma, Hodgkin lymphoma, chronic lymphocytic leukemia, or multiple myeloma and baseline hemoglobin of 10 to 12 g/dL who were scheduled for $\geq$4 months of myelosuppressive chemotherapy were randomized to receive $\leq$16 weeks of epoetin alfa at a dose of 40,000 U once weekly immediately (early) or to wait and only receive epoetin alfa if hemoglobin decreased to <9 g/dL (late). Those patients with a hemoglobin level >12 g/dL after 3 chemotherapy cycles were not randomized. The primary endpoint was a mean change in the Functional Assessment of Cancer Therapy-Anemia (FACT-An) total.

**RESULTS.** In all, 269 patients with a hemoglobin level $\leq$12 g/dL were randomized. The mean total FACT-An increased 3.84 (95% confidence interval [95% CI], 0.21–7.46) in early patients and decreased 4.37 (95% CI, −7.99 to −0.74) in late patients ($P = .003$). Early patients had significantly ($P < .05$) higher mean scores for total FACT-General; FACT-General physical and functional well-being subscales, total anemia scale, and fatigue subscale; and daily activity, energy, and important activity Linear


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Analog Scale Assessment scales, as well as reduced bedrest days and restricted activity days. The mean hemoglobin increased 1.2 g/dL (95% CI, 0.98–1.46) in early patients but decreased 0.2 g/dL (95% CI, −0.32–0.12) in late patients ($P < .0001$). Adverse events were similar between groups (with fatigue being the most prevalent); clinically relevant thromboembolic events were more common in early patients.

**CONCLUSIONS.** Treating mild anemia immediately with epoetin alfa during chemotherapy for hematologic malignancy significantly improved QOL, productivity, and hemoglobin compared with delaying treatment until the hemoglobin level decreases to <9.0 g/dL. ***Cancer*** **2006;107:1909–17.** © *2006 American Cancer Society.*

**KEYWORDS: anemia, epoetin alfa, hematologic malignancies, quality of life, productivity.**

It is estimated that approximately 70% of patients with hematologic malignancies develop cancer-related or chemotherapy-related anemia (CRA) (a hemoglobin [Hb] level ≤12 g/dL).[1] Fatigue, the hallmark symptom of anemia (although it may have a multifactorial etiology beyond low Hb levels[2]), is reportedly a major contributor to impaired quality of life (QOL) in cancer patients.[3–5] In cancer patients with anemia, correlations between the Hb level and QOL have been documented.[6] Community trials of epoetin alfa during chemotherapy ± radiotherapy demonstrated that the greatest QOL improvement occurs when Hb increases from 11 g/dL to 12 g/dL,[7] or with increases of 2 g/dL to 4 g/dL.[8] However, to our knowledge controlled trials have not defined the optimal timing of epoetin alfa with respect to improving QOL,[9] and clinical practice guidelines differ regarding when to initiate anemia treatment in patients with cancer and mild anemia.[10,11]

Erythropoietic agents significantly decrease transfusion requirements, increase Hb, and improve QOL in anemic patients with solid tumors and hematologic malignancies who are being treated with chemotherapy ± radiotherapy.[12–15] Because the clinical benefits of treating mild anemia are not well known, the objective of the current study was to compare immediate epoetin alfa for mild anemia with treatment that was delayed until moderate anemia developed during chemotherapy for hematologic malignancies. The intent was to detect differences between early and late treatment with respect to patient-perceived QOL, which is a more subtle outcome than a reduction in transfusion requirements (regarded, from a regulatory standpoint, as the "gold standard" endpoint of erythropoietic therapy). While recognizing the inherent limitations of an open-label design without a placebo arm, a double-blind, placebo-controlled design was considered impractical given that epoetin alfa was already approved in the U.S. for treating CRA at the time of study initiation.

## MATERIALS AND METHODS

### Study Design and Patients

This randomized, open-label, multicenter clinical trial was conducted at 20 U.S. academic institutions between December 1997 and November 2002. Randomization was balanced using 4 permuted blocks and stratified by center. Patients with histologically confirmed non-Hodgkin lymphoma, Hodgkin lymphoma, chronic lymphocytic leukemia, or multiple myeloma were eligible if they met the following inclusion criteria: age ≥18 years, an assessable lesion, were scheduled to receive myelosuppressive chemotherapy for ≥4 months, an Hb level ≥10 g/dL, adequate iron stores (transferrin saturation ≥20% and serum ferritin ≥50 μg/L), a Karnofsky performance status (PS) ≥70, and a life expectancy ≥6 months. Patients were excluded for a second active malignancy or history of other malignancy within 5 years; human immunodeficiency virus infection; uncontrolled hypertension; active infection; anemia from factors other than cancer or chemotherapy; receipt of chemotherapy within 14 days or epoetin alfa independent of protocol; prior total lymphoid, extensive abdominal, or inverted Y radiation; or the prolonged use of interferons or interleukins during the study. Each institutional review board approved the protocol and all patients provided written informed consent.

### Treatment

Patients were enrolled with an Hb level ≥10 g/dL. Those with an Hb level ≥10 g/dL to ≤12 g/dL were randomly assigned 1:1 to immediate epoetin alfa (early group) or to observation potentially followed by delayed treatment with epoetin alfa when the Hb level decreased to <9 g/dL (late group). Patients with an entry Hb level of >12 g/dL were enrolled but randomized only if the Hb level decreased to ≤12 g/dL during chemotherapy. Early patients received epoetin alfa (Procrit; Ortho Biotech Products, L.P., Bridgewater, NJ) once weekly immediately after randomization. Late patients received no

epoetin alfa for 6 weeks (3-week-cycle chemotherapy) or 8 weeks (4-week-cycle chemotherapy) and then received epoetin alfa only if the Hb level was <9 g/dL. Epoetin alfa at a dose of 40,000 U was given subcutaneously once weekly for ≤16 weeks, with dose escalation to 60,000 U weekly if no Hb increase >1.0 g/dL was observed within 3–4 weeks. If the Hb level increased to >15 g/dL on 2 consecutive evaluations, epoetin alfa was withdrawn. If the Hb level subsequently decreased to <13 g/dL, treatment was resumed. Patients whose Hb never decreased to ≤12 g/dL by Week 9 (3-week-cycle group) or Week 12 (4-week-cycle group) did not qualify for randomization and were dropped from the study.

### Study Assessments

Assessments within the 10-day preenrollment period included medical history, physical examination, complete blood count and biochemistry panel, reticulocyte count, serum ferritin, iron, total iron-binding capacity, serum folate, vitamin $B_{12}$, Karnofsky PS, self-reported QOL, and healthcare utilization and work/productivity. Tumor stage was assessed within 8 weeks of randomization, and transfusion history was obtained for the preceding 6 months. Evaluation was based on patients' chemotherapy cycles (every 3 weeks or 4 weeks) and included repeated laboratory studies, blood pressure, transfusion record since the last visit, changes in chemotherapy or radiotherapy, adverse events (AEs), self-reported QOL, healthcare utilization, and work/productivity.

The following questionnaires were administered during the clinic visits: Functional Assessment of Cancer Therapy-Anemia (FACT-An) total, which includes the FACT-General (FACT-G) scale consisting of physical, functional, emotional, and social/family well-being subscales (27 items),[16] and the anemia scale consisting of fatigue (13 items) and nonfatigue (7 items) subscales.[17,18] Four 100-mm Linear Analog Scale Assessments (LASA) represented energy, daily activity, important activity, and overall QOL. Healthcare utilization (hospitalizations, clinic visits, nurse visits, calls to physician, and general assistance visits) and productivity (bedrest days, reduced activity days, patient and caregivers' missed-work days) were reported by the patient based on prior month and week recall.[19] For example, a reduction in the number of days in bed was assessed by the following question: Were there any days during the past week (past 7 days) when your illness, treatment, or a personal or emotional problem (like feeling depressed) caused you to stay in bed half a day or more? If the answer was yes, the number of days was to be written in.

The primary study endpoint was change in QOL on the total FACT-An. Secondary endpoints were changes in LASA, healthcare utilization, and work and role productivity. Additional clinical endpoints were Hb change and hematologic response (increase in the Hb level ≥2.0 g/dL or Hb ≥12 g/dL), transfusion requirements, tumor response (evaluated at baseline and at the time of study completion or early withdrawal), time spent with the Hb level at >10 and >12 g/dL, and safety. Safety was monitored by AE reporting and laboratory assessments; deaths occurring before or within 30 days of the last study visit were recorded. Overall survival was not an endpoint, but survival was recorded for patients entered into the study for the accrual duration.

### Statistical Analysis

Subjects were evaluated for QOL if they had a baseline and ≥1 postrandomization measure. Because of the variable follow-up duration among patients, continuous measures and scales were modeled using the random coefficient linear growth curve model: $Y = X\beta + Zb + \varepsilon$ ($Y$ is the vector of postrandomization responses; $X$ is fixed effects, including baseline measure, treatment group, and week of visit [week]; and $Z$ is random linear growth trajectory parameters). The model was fitted using SAS Proc Mixed software (SAS Institute, Inc., Cary, NC) and parameters were estimated by restricted maximum likelihood, with treatment effect representing mean differences between treatments after adjusting for baseline response and individual growth trajectories. Outcome measures associated with employment, work loss, bedrest days, days of restricted activities, and healthcare utilization were fitted to a generalized linear model for longitudinal data, assuming Poisson distribution, and estimation was performed using generalized estimating equations in SAS Proc Genmod software. Missing responses for individual items were replaced by the mean score of all nonmissing items within the specified subscale for that subject, provided the number of nonmissing items was ≤50% of the total number of items for that scale. Subscales with >50% missing items were excluded from analyses. The percentage of scales with ≥15% of items missing on the FACT-An was only 1.5% and, as such, the imputation methods were considered valid. For all comparisons, $P < .05$ was considered statistically significant and $P$-values for secondary endpoint subscale analyses were not adjusted for multiple endpoints. All randomized patients were included in the analysis of the additional clinical endpoints cited in the previous section as well as safety. Post hoc secondary analyses were performed for thromboembolic events (TVEs).

The sample size of 260 evaluable patients was prospectively determined based on validation data[17] to be adequate to detect a 3-point difference (representing a 0.35 effect size) between the 2 groups in the

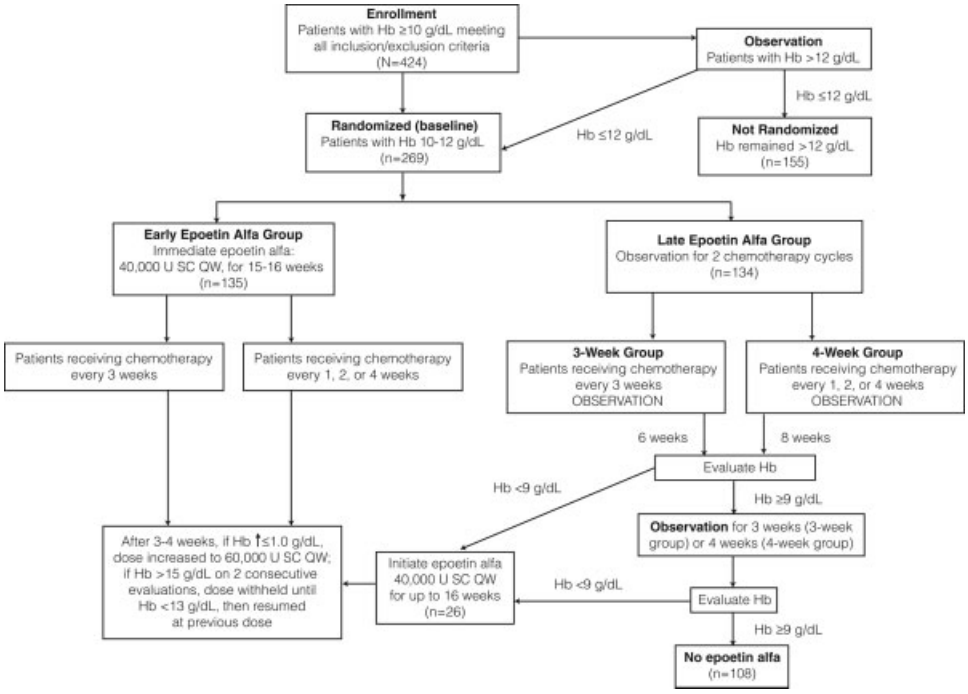


**FIGURE 1.** Treatment schema. Hb indicates hemoglobin; SC, subcutaneously; QW, once weekly; up arrow, increase.

change in the FACT-An Anemia subscale with 80% power, given a 2-sided $\alpha$ of 0.05 and a within-group standard deviation of 8.5 points.

## RESULTS

### Study Accrual and Follow-up

Of the 424 patients enrolled, 135 were randomized to the early group and 134 to the late group (Fig. 1). The 155-patient nonrandomized subset was similar to the randomized arms in that 84% of patients had non-Hodgkin lymphoma, but it consisted of more females (73%) and had a lower mean age (51.7 years). Baseline and $\geq$1 follow-up questionnaire were completed by 119 early patients and 113 late patients. The median study duration was 105 days and 111 days, respectively, for early and late patients. In the late group ($n$ = 134 patients), 26 patients (19.4%) received epoetin alfa because their Hb level decreased to <9 g/dL and 108 patients (80.6%) did not receive epoetin alfa. There were no significant between-group differences noted with regard to baseline patient characteristics (Table 1), baseline QOL, or healthcare utilization and productivity.

**TABLE 1**
**Baseline Patient Characteristics**

| Variable | Early ($n$ = 135) | Late ($n$ = 134*) |
|---|---|---|
| Age, y | | |
| Mean ± SD | 59.0 ± 14.0 | 60.5 ± 14.9 |
| Range | 20–84 | 23–88 |
| Sex, no. (%) | | |
| Male | 70 (51.9) | 70 (52.2) |
| Female | 65 (48.1) | 64 (47.8) |
| Race, no. (%) | | |
| White | 103 (76.3) | 100 (74.6) |
| Hispanic | 16 (11.9) | 19 (14.2) |
| Black | 10 (7.4) | 9 (6.7) |
| Other | 6 (4.4) | 6 (4.5) |
| Malignancy, no. (%) | | |
| Non-Hodgkin lymphoma | 114 (84.4) | 115 (85.8) |
| Multiple myeloma | 8 (5.9) | 9 (6.7) |
| Hodgkin disease | 7 (5.2) | 5 (3.7) |
| Chronic lymphocytic leukemia | 6 (4.4) | 5 (3.7) |
| Hemoglobin, g/dL, mean ± SD | 11.1 ± 0.7 | 11.2 ± 0.7 |
| Karnofsky performance status, mean ± SD | 87.3 ± 8.0 | 88.3 ± 7.4 |
| Chemotherapy-naive, no. (%)† | 90 (67.2) | 91 (67.9) |

SD indicates standard deviation.

* 26 patients treated with epoetin alfa and 108 patients who did not receive epoetin alfa.

† Data were missing for 1 early patient.

### Hematologic Measures

The mean Hb level (95% confidence interval [95% CI]) increased significantly during chemotherapy by 1.2 g/dL (95% CI, 0.98–1.46 g/dL) in early patients and decreased by 0.2 g/dL (95% CI, −0.32–0.12 g/dL) in late patients ($P$ < .0001 between groups). More early versus late patients achieved a hematologic response (70.4% vs. 25.4%; $P$ < .0001). Hb increased by approximately 1.0 g/dL during the first month for early patients and was significantly ($P$ < .0001) higher after the first month compared with late patients (Fig. 2). Significantly fewer early patients had their Hb level decrease to <10 g/dL during the study (25.2% vs.

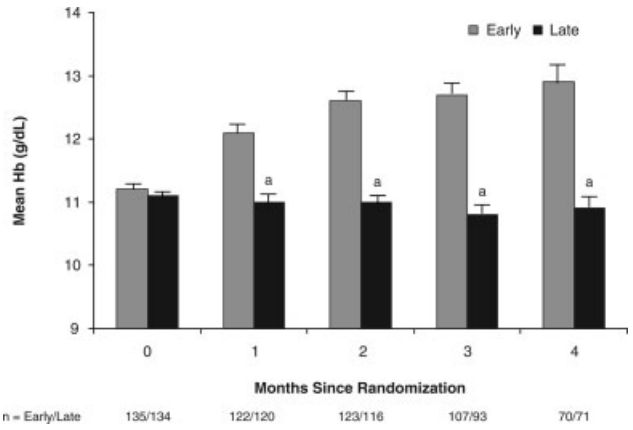


**FIGURE 2.** Mean hemoglobin (Hb) change (intent-to-treat; $n = 269$). [a]$P <$ .0001 early versus late group. Postrandomization Months 1, 2, 3, and 4 values correspond with mean Hb between Weeks 0 (baseline) to Weeks 4, 5–9, 10–14, and 15–20, respectively.

44.8%; $P < .001$). The percentage of days with a Hb level >10 and >12 g/dL was significantly higher for early patients compared with late patients (86.7% vs. 75% [$P < .02$] and 65.1% vs. 21.6% [$P < .001$], respectively).

### QOL

Mean FACT-An and LASA changes (reflecting the difference between the treatment period averages and baseline values for each subject) are presented in Table 2. The mean change in the total FACT-An favored early patients by 8.2 points ($P = .003$) (Fig. 3A). Mean changes also favored early patients for the anemia subscale of the FACT-An (3.6-point difference; $P = .008$) and for the fatigue component of this subscale (3.1-point difference; $P = .005$), as well as for the total FACT-G ($P = .013$) and its domains of physical ($P = .007$) and functional ($P = .024$) well-being (Fig. 3B). The magnitude of the mean treatment differences for the total FACT-An, fatigue component of the FACT-An anemia subscale, and total FACT-G subscale, respectively, are considered clinically significant.[20,21] No change in any FACT scale favored late patients.

Early patients had significantly more improved scores for LASA daily activity ($P = .008$), energy ($P = .007$), and important activity ($P = .045$) (Fig. 3C). No change in any LASA scale favored late patients.

The associational link between epoetin alfa treatment and beneficial QOL effects was demonstrated by significant ($P < .05$) correlations between treatment-related changes in the Hb level and changes in the total FACT-An, total FACT-G, FACT-G functional well-being subscale, FACT-An anemia scale, FACT-An fatigue and nonfatigue subscales, and LASA daily activity and overall QOL (Table 2).

### Healthcare Utilization and Work/Productivity

Compared with late patients, early patients had significantly greater reductions in days spent in bed (52.2% vs. 3.1%; $P = .017$) and restricted activity days (41.6% vs. 12.2%; $P = .042$). Early patients had numerically greater reductions in the number of nights spent in the hospital, clinic visits, calls to physicians, and patients' and others' missed work days ($P$-values not significant).

### Transfusions and Tumor Response

There was no significant difference noted between the groups in the percentage of patients requiring red blood cell transfusion (17.8% and 26.1% of early and late patients, respectively; $P = .11$). There were 23 complete tumor responses per group.

### Safety

AEs with an incidence of >20% were similar between groups (Table 3), with fatigue being the most common AE. Overall, serious AEs, not necessarily associated with epoetin alfa, were experienced by 41% and 31% of early and late patients, respectively, with fever and neutropenia reported to be the only 2 events with an incidence ≥5% in both groups. On-study mortality (+30 days) was experienced by 3 early patients (all of whom received epoetin alfa) and 4 late patients (none of whom received epoetin alfa). None of the deaths in the early group were classified by the clinical site or principal investigator as being related to epoetin alfa.

Clinically relevant TVEs were more common in early patients (Table 3). Based on the definitions specified on the AE form, clinically relevant TVEs were diagnosed in 15 early patients (11.1%) (deep thrombophlebitis in 8 patients and embolism in 3 patients, 2 of which were specified as a pulmonary embolism (PE)], cerebrovascular disorder in 2 patients, unspecified thrombosis in 1 patient, and myocardial infarction in 1 patient) and 4 late patients (3.0%) (cardiac arrest in 2 patients, PE in 1 patient, and cerebrovascular disorder in 1 patient) ($P = .015$ between groups). Two of the TVEs reported in the late group (cardiac arrest and PE) occurred in patients who had received epoetin alfa. Overall, of the 19 clinically relevant TVEs reported in the randomized safety population, 17 occurred among patients receiving epoetin alfa.

When the groups were combined and patients were stratified by peak Hb 1) ≥13 g/dL or <13 g/dL, and 2) ≥12 g/dL or <12 g/dL in 2 separate post hoc analyses, the TVE incidence was not found to be correlated with a higher Hb level. TVEs occurred in 10 of 141 patients with a peak Hb level ≥13 g/dL compared with 9 of 128 patients with an Hb level that was never

**TABLE 2**
**Changes in Mean Quality-of-Life Scores and Correlations with Hb Changes**

| Scale (no. of items) | Early ($n$ = 119) Mean (SE) | Late ($n$ = 113) Mean (SE) | Unadjusted mean (SE) between-group difference | Estimated mean (SE) between-group difference* | $P$ between groups* | $R$ change in Hb and scale† | $P$ for $R$ |
|---|---|---|---|---|---|---|---|
| **FACT-Anemia** | | | | | | | |
| FACT-General (27) | | | | | | | |
| Physical well-being (7) | +1.0 (0.42) | −0.33 (0.45) | 1.33 (0.61) | 1.24 (0.46) | 0.007 | 0.082 | 0.217 |
| Functional well-being (7) | +0.43 (0.38) | −1.03 (0.45) | 1.46 (0.58) | 1.11 (0.49) | 0.024 | 0.203 | 0.002 |
| Emotional well-being (6) | +0.64 (0.29) | +0.03 (0.29) | 0.62 (0.41) | 0.33 (0.36) | 0.360 | 0.026 | 0.692 |
| Social/family well-being (7) | −0.43 (0.38) | −0.67 (0.30) | 0.23 (0.49) | −0.08 (0.41) | 0.840 | 0.084 | 0.202 |
| Total FACT-General scale | +1.74 (0.98) | −2.37 (0.93) | 4.11 (1.37) | 3.01 (1.21) | 0.013 | 0.166 | 0.011 |
| Anemia subscale (20) | | | | | | | |
| Fatigue (13) | +1.45 (0.77) | −1.68 (0.87) | 3.13 (1.16) | 2.67 (0.94) | 0.005 | 0.133 | 0.043 |
| Nonfatigue (7) | +0.54 (0.29) | −0.03 (0.31) | 0.57 (0.42) | 0.61 (0.34) | 0.078 | 0.145 | 0.027 |
| Total anemia subscale | +1.92 (0.97) | −1.71 (1.1) | 3.63 (1.44) | 3.18 (1.19) | 0.008 | 0.146 | 0.026 |
| Total FACT-anemia (FACT-General + anemia subscale; 47) | +3.84 (1.85) | −4.37 (1.85) | 8.22 (2.62) | 6.67 (2.25) | 0.003 | 0.178 | 0.007 |
| **LASA** | | | | | | | |
| Daily activities (1) | +2.88 (1.88) | −3.87 (2.03) | 6.75 (2.75) | 5.96 (2.23) | 0.008 | 0.158 | 0.016 |
| Energy (1) | +3.22 (1.84) | −4.26 (2.06) | 7.49 (2.75) | 6.03 (2.24) | 0.007 | 0.120 | 0.071 |
| Important activities (1) | +2.15 (2.35) | −3.6 (2.47) | 5.72 (3.41) | 5.37 (2.67) | 0.045 | 0.097 | 0.149 |
| Overall quality of life (1) | +3.27 (2.0) | −0.79 (1.86) | 4.1 (2.72) | 3.11 (2.13) | 0.146 | 0.158 | 0.016 |

Hb indicates hemoglobin; SE, standard error; FACT, Functional Assessment of Cancer Therapy; LASA, Linear Analog Scale Assessment; +, improvement; −, worsening.

* Based on the treatment effect using a random coefficient linear growth curve model.

† Pearson correlation coefficient between change in Hb and change in quality-of-life scale or score.

>13 g/dL (7.1% vs. 7.0%; $P = 1.00$) and in 16 of 207 patients with a peak Hb level ≥12 g/dL compared with 3 of 62 patients with an Hb level that was never >12 g/dL (7.7% vs. 4.8%; $P = .58$). Similar post hoc analyses within the individual groups likewise failed to demonstrate correlations between a peak Hb level ≥13 g/dL or ≥12 g/dL and an increased incidence of TVE in early or late patients (data not shown).

When the groups were combined and only those patients who received epoetin alfa were stratified by the aforementioned peak Hb levels, again, there were no significant correlations noted between TVE incidence and a higher Hb level. TVEs occurred in 11 of 103 patients treated with epoetin alfa with a peak Hb level ≥13 g/dL compared with 7 of 58 patients with an Hb level that was never >13 g/dL (10.7% vs. 12.1%; $P = .80$) and in 17 of 135 patients with a peak Hb level ≥12 g/dL compared with 1 of 26 patients with a Hb level that was never >12 g/dL (12.6% vs. 3.9%; $P = .31$).

## DISCUSSION

The current study compared 2 epoetin alfa treatment algorithms for patients with hematologic malignancies, and demonstrated a consistent and meaningful QOL advantage for treating mild anemia earlier during chemotherapy. Patients with mild anemia receiving epoetin alfa at the time of chemotherapy initiation had a significant increase in Hb, with corresponding improvements in physical-specific, functional-specific, and fatigue-specific QOL scores and reductions in bed and restricted activity days compared with patients whose anemia treatment was delayed until the Hb level was <9 g/dL. More early-treated compared with late-treated patients achieved a hematologic response and spent more time with an Hb level >12 g/dL (current guidelines suggest a target Hb range not to exceed 12 g/dL[10,11]). Although transfusion and chemotherapy-induced complete response rates were similar between the groups, this study was not sufficiently powered or expected to demonstrate differences in these secondary endpoints. Transfusion rates were low in both arms, as expected given that the population was comprised of patients with good PS and a relatively high mean baseline Hb level. Tumor response rates and other chemotherapy-specific issues such as dose intensity would be difficult to interpret in such a heterogeneous group who had various malignancy types and were undergoing various anticancer therapies.

An association between Hb and QOL was supported by our results demonstrating that Hb increases were positively although weakly correlated with improvements in the QOL. In this regard, improved QOL

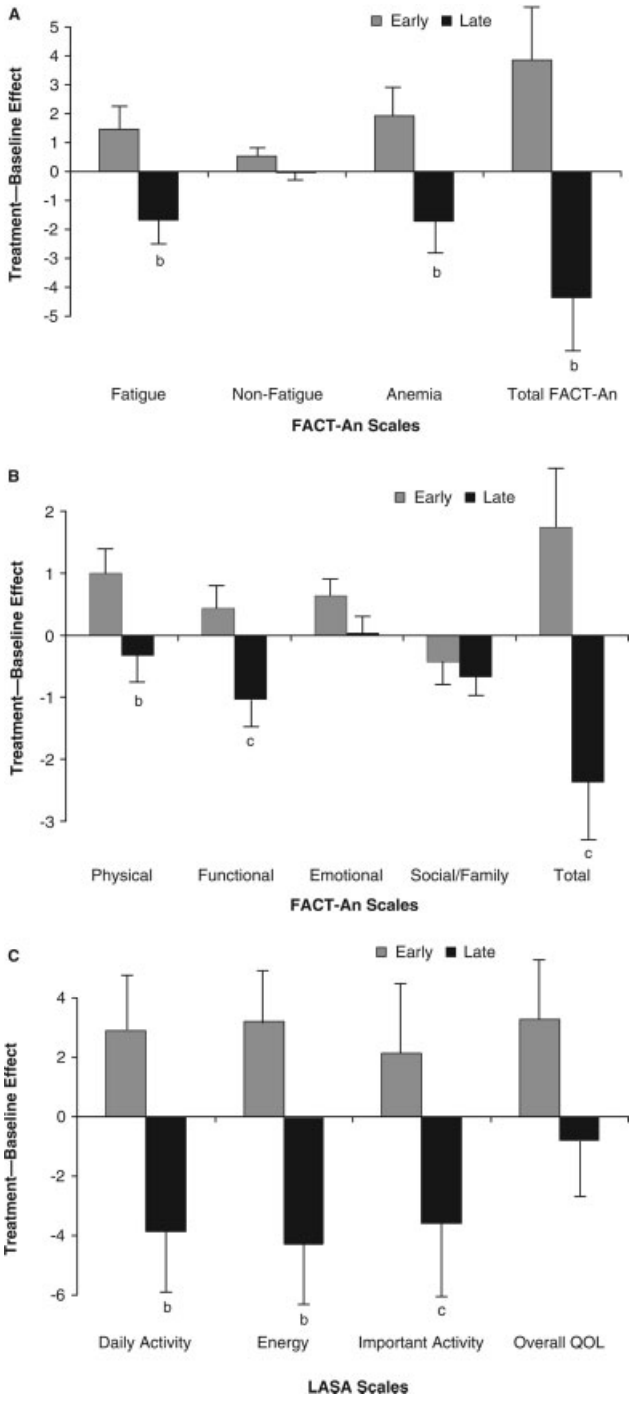


**FIGURE 3.** Mean treatment effects[a] for the (A) FACT-An scale, (B) FACT-G scale, and (C) LASA. FACT-An indicates Functional Assessment of Cancer Therapy-Anemia; FACT-G, Functional Assessment of Cancer Therapy-General; LASA, Linear Analog Scale Assessment. [a]Average quality of life/function during chemotherapy relative to baseline. [b]$P < .01$ late vs. early treatment. [c]$P < .05$ late vs. early treatment.

**TABLE 3**
**Safety Results**

| | No. of patients (%) | |
|---|---|---|
| | Early ($n$ = 135) | Late ($n$ = 134) |
| Adverse events in ≥20% of patients* | | |
| Fatigue | 81 (60.0) | 81 (60.4) |
| Nausea | 68 (50.4) | 66 (49.3) |
| Granulocytopenia | 59 (43.7) | 62 (46.3) |
| Alopecia | 52 (38.5) | 45 (33.6) |
| Constipation | 53 (39.3) | 45 (33.6) |
| Fever | 56 (41.5) | 54 (40.3) |
| Coughing | 46 (34.1) | 43 (32.1) |
| Vomiting | 37 (27.4) | 30 (22.4) |
| Insomnia | 35 (25.9) | 35 (26.1) |
| Pain | 44 (32.6) | 35 (26.1) |
| Diarrhea | 40 (29.6) | 31 (23.1) |
| Rhinitis | 38 (28.1) | 27 (20.1) |
| Headache | 31 (23.0) | 21 (15.7) |
| Abdominal pain | 40 (29.6) | 27 (20.1) |
| Dyspnea | 29 (21.5) | 37 (27.6) |
| Back pain | 25 (18.5) | 28 (20.9) |
| Anorexia | 37 (27.4) | 24 (17.9) |
| Hypokalemia | 26 (19.3) | 29 (21.6) |
| Dizziness | 27 (20.0) | 21 (15.7) |
| Pharyngitis | 28 (20.7) | 10 (7.5) |
| Dyspepsia | 18 (13.3) | 29 (21.6) |
| Thrombocytopenia | 27 (20.0) | 21 (15.7) |
| Clinically relevant thromboembolic events | 15 (11.1) | 4 (3.0) |

* Each report represents ≥1 event per patient.

could have stemmed from other factors, including chemotherapeutic response or cognitive improvements correlated with hemoglobin response to epoetin alfa that could also be partly mediated through erythropoietin receptors in the brain.[22] The potential involvement of such non-Hb mediators could explain why only a limited and nonsignificant difference in transfusion requirements was noted.

It is difficult to directly translate QOL differences between groups into practical consequences for individual patients.[23,24] However, all mean differences exceeded the clinically meaningful thresholds established by Cella et al.[20] and Patrick et al.[21] The mean relative improvement of 8.2 points for the total FACT-An scale (1.2 points higher than the 7-point individual patient threshold) for early versus late patients implies that the number of individuals benefiting by early intervention would be substantial. Changes in treatment algorithms and guidelines to improve quality of care are often implemented when greater benefit can be assured for a significant portion of the patient population and, although QOL thresholds are typically established for determining clinical benefit for individual patient care, when the standard is applied to

mean treatment differences in clinical and healthcare populations,[25] the practical quality-of-care implications are even more compelling. For example, an 8.2-point mean relative FACT-An improvement does not equate to an individual patient given early or late treatment experiencing a mean difference of 8.2 points, but rather that the full impact of this treatment differential will be experienced more frequently in a given population receiving early versus late treatment.[25] Therefore, even treatment differences appearing small can have large clinical impacts.

Most AEs were comparable between the groups and attributed to either chemotherapy or disease and not to epoetin alfa; however, there was a higher TVE rate among early patients. This study was designed before 2 studies suggesting increased mortality and venous thromboembolism rates during erythropoietic therapy were published,[26,27] and therefore did not include formal prospective assessments for this particular AE. Subsequent analyses of both trials did not provide clear explanations for the unexpected survival data, and the relative contributions of TVE-related mortality remain unclear; nonetheless, the labeling for erythropoietic agents has been revised to recommend a target Hb level $\leq$12 g/dL. A metaanalysis of randomized controlled trials of erythropoietic therapy originally found no negative effects on overall survival or the risk of TVE-related complications among patients with cancer- or treatment-related anemia[28]; however, a subsequently published update demonstrated a significant increase in TVEs (relative risk, 1.67; 95% CI, 1.35–2.06) and an uncertain impact on mortality (relative risk, 1.08; 95% CI, 0.99–1.18).[29] Of note, for the current study, post hoc analyses did not demonstrate any correlation between a higher Hb level (using an Hb level of 12 g/dL or 13 g/dL as the cutoff) and increased TVE risk. Nonetheless, research efforts to elucidate the effect of erythropoietic therapy on survival and TVE risk in the cancer population continue.

The primary study limitation is a possible response bias effect from the open-label design. However, with a double-blind, placebo-controlled design, we believe that it would have been difficult to ask patients to subject themselves to a randomization in which they might receive placebo rather than epoetin alfa, an agent approved and available for treating chemotherapy-induced anemia at the time the trial was opened. Because patients were not blinded, it is reasonable to question whether the between-group differences were due to response bias commonly associated with open-label studies, including "social desirability" and "faking good."[30] We attempted to limit bias by disguising socially desirable or good answers through the use of validated scales. Patients were not simply asked whether they improved or not; rather, multiple scales were computed using responses from hundreds of individual questions collected longitudinally during many visits separated by 3 to 4 weeks. Under these conditions, the possibility that a patient would be able to fake an improvement is largely reduced. In addition, observed treatment effects were more specific and larger for anemia-related fatigue relative to more generic QOL scales, arguing against a large response bias effect. We also demonstrated a positive correlation between Hb changes and QOL changes (as previously documented in cancer patients assessed via the FACT-An[6]) independent of treatment assignment, with patients receiving epoetin alfa not experiencing an increased Hb level having similar QOL outcomes as those not receiving epoetin alfa, thereby serving as further evidence that patients were reporting truthfully. From a clinical practice standpoint, another potential limitation is that the Hb limit chosen for treatment might have been too low according to current practice standards. Because our study was designed in 1997, predating the most recent evidence-based clinical practice guidelines for treating cancer- or cancer treatment-related anemia,[10,11] the Hb level was allowed to decrease to <9 g/dL. Finally, long-term survival data were not collected, which can be considered a limitation in the current era in which the impact of erythropoietic therapy on survival has not been clearly elucidated.

Our QOL and clinical results support treating mild anemia with epoetin alfa during chemotherapy for hematologic malignancies. These findings have implications for quality-of-care and treatment guidelines as well as future research to explore potential economic benefits associated with improvements in these outcomes.

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