Epoetin Alfa Improves Quality of Life in Patients with Cancer

Results of a Metaanalysis

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BACKGROUND. Anemia in patients with cancer causes fatigue, weakness, and impaired concentration, negatively impacting quality of life (QOL). In clinical trials involving patients with cancer who had varied characteristics, it has been shown that epoetin alfa treatment increased hemoglobin levels and improved QOL. A systematic review and metaanalysis of data from those trials was conducted to summarize existing knowledge on the role of epoetin alfa in improving QOL for anemic patients with cancer.

METHODS. The Cochrane Library and other data bases were searched for published and unpublished, randomized/controlled and single-arm studies that included ≥ 20 patients with cancer per arm, epoetin alfa treatment, and QOL assessment by Cancer Linear Assessment Score (CLAS), Functional Assessment of Cancer Therapy (FACT) scale, Eastern Cooperative Oncology Group (ECOG) scale, and/or Medical Outcomes Study Short-Form 36 (SF-36) scale.

RESULTS. Among 11,459 patients from 23 trials, epoetin alfa and control cohorts were indistinguishable (with regard to demographic, clinical, QOL variables) at baseline. Epoetin alfa improved CLAS (20–25%), FACT-Fatigue (17%), and FACT-Anemia (12%) scores ($P = 0.05$). ECOG scores worsened for control cohorts ($P = 0.05$); epoetin alfa cohorts remained unchanged. Four of the SF-36 subscales, Physical Function, Role Physical, Vitality, and Social Function, improved with epoetin alfa ($P = 0.05$). Results adjusted for confounding factors remained consistent.

CONCLUSIONS. This metaanalysis confirmed that epoetin alfa improves QOL significantly in patients with cancer, emphasizing the need to manage anemia in this population. ***Cancer* 2004;101:1720–32.** © *2004 American Cancer Society.*

KEYWORDS: anemia, chemotherapy, epoetin alfa, metaanalysis, quality of life.

Anemia is a common problem in patients with cancer who receive chemotherapy.[1–3] Despite the high prevalence of anemia in patients with cancer and the correlation of low hemoglobin levels and poor performance status, few patients with cancer receive treatment for anemia.[4] Anemia and its effects interfere with effective treatment, which can lead to poorer clinical outcomes.[5–8] One of the most common consequences associated with anemia is fatigue, which occurs in 58–90% of patients with cancer[9–14] and can be more distressing and disruptive to ordinary activity even than disease-associated pain.[10,13,15] Other common effects include exhaustion, weakness, and impaired concentration.[5,16–18] All of these factors have a negative impact on the quality of life (QOL) of patients with cancer.[5,10,14] Patients who face disease-related debilitation and comorbidities present challenges as participants in rigorous clinical trials due to the

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difficulties of participating and the frequent presence of confounding factors[15]; the various anemia-associated symptoms and their respective roles in diminished QOL, for the most part, are understood poorly and have been under-investigated.[5,10,14,15]

Recombinant human erythropoietin (epoetin alfa) is identical to human erythropoietin, which is a hematologic growth factor, and has been shown in clinical trials to correct and prevent anemia, decrease the need for blood transfusion, and improve the QOL of patients with cancer.[7,19–29] Recently, large trials involving patients receiving chemotherapy for cancer have demonstrated that the QOL benefits of epoetin alfa 150 IU/kg administered 3 times per week[7,26,27] or 40,000 IU once weekly[28] are related directly to the epoetin alfa-stimulated increase in red blood cell production.

The study described here is a metaanalysis of 23 randomized controlled trials (RCTs) and single-arm studies in which epoetin alfa was given to patients with cancer; QOL scores were measured throughout the study. Because the effect of this agent on QOL has not been accepted widely, and many patients who could benefit from anemia treatment do not receive it, this metaanalysis was designed to evaluate the role of epoetin alfa in improving QOL in patients receiving chemotherapy for cancer based on results of published and unpublished data.

MATERIALS AND METHODS

Search Strategy and Selection Criteria

MEDLINE®, EMBASE®, Ovid, the Cochrane Library, and Adis were searched for all articles published from 1985 to 2002, according to a written protocol. Articles with the following text words (tw) or Medical Subject Headings (MeSH®) in their titles, abstracts, or keyword lists were examined: erythropoietin (tw, MeSH), epoetin alfa (MeSH), epoetin (tw), Epogen (tw), Procrit® (tw), Eprex® (tw), epo (tw), anemia/drug therapy (MeSH, all subheadings), anemia/therapy (MeSH, all subheadings), or anemia/diet therapy (MeSH, all subheadings). Search results were limited to articles on human subjects indexed under the MeSH terms *neoplasms* or *myelodysplastic syndromes* (all subheadings). The data base search yielded 125 published abstracts. A number of unpublished internal reports were received directly from Johnson & Johnson Pharmaceutical Research and Development (Raritan, NJ).

Preliminary references were then examined to determine whether they met the inclusion criteria identified in the study protocol. Randomized control and single-arm, open-label studies of epoetin alfa with $\geq$ 20 patients per study group who were diagnosed with cancer, and/or who were receiving chemotherapy, and who reported $\geq$ 1 of the validated QOL measures that had been identified as being reported in sufficient studies were examined further. Only articles that met all of these inclusion criteria were accepted for this metaanalysis. In many cases, the full articles were retrieved to determine whether the acceptable QOL measures were reported. Articles in languages other than English were translated by a qualified translation service (Australian Institute of Modern Language, Waverley, New South Wales, Australia).

Health-Related QOL Scales

The study protocol was written to include a wide variety of QOL scales (some generic and some cancer-specific), which assessed factors including activity, fatigue, and energy that contribute to the decreased QOL experience of patients with cancer. A search was undertaken to include as many different QOL scales as possible. The QOL scales were included if results were reported in three or more references and if the scales were validated and in common usage. Four separate QOL scales were included that met these two criteria: the Cancer Linear Analog Scale (CLAS); the Functional Assessment of Cancer Therapy (FACT) scale; the Eastern Cooperative Oncology Group (ECOG) scale; and the Medical Outcomes Study Short Form-36 (SF-36) scale.

The CLAS and FACT scales were developed specifically to measure cancer QOL[30] and constitute the primary variables in this metaanalysis. CLAS scores were reported as either CLAS or Linear Analog Scale Assessment (LASA) scores in the original reports; but they have been treated as equivalent in this metaanalysis, because they ask respondents (patients) to address the same question on the same recording instrument (a 100-mm line). The three CLAS subscales are 1) Activity; 2) Energy; and 3) Overall QOL. The FACT-General (FACT-G) has four subscales that measure physical, functional, emotional, and social well being and can be augmented by the use of other subscales (FACT-Fatigue [FACT-F], FACT-Anemia [FACT-An]) that measure fatigue and anemia, respectively. The ECOG scores are cancer-specific and were reported as either ECOG scores or World Health Organization (WHO) performance status scores in the original reports. A review of these two physician-reported scales indicated that they used the same anchors and were identical otherwise; hence, they have been treated as equivalent in this metaanalysis.[31,32] The SF-36 is a generic QOL patient questionnaire that is used widely in health-related research.[33] Sufficient data were reported for eight SF-36 subscales to be reviewed: 1) Physical Function, 2) Role Physical, 3)

Pain, 4) General Health, 5) Vitality, 6) Social Function, 7) Role/Emotion, and 8) Mental Health.

Data Extraction

Data items were evaluated across publications to ensure that they were sufficiently common to warrant inclusion. Two surveyors independently extracted data onto a data-extraction form. The surveyors then compared data extractions and resolved any discrepancies by referral to the original publications. The data were then entered into a computer data base.

Metaanalysis

The primary objective of the metaanalysis was to compare QOL for patients receiving epoetin alfa with QOL for control patients. The three main analyses were 1) unadjusted, combined estimates of findings across studies; 2) estimates stratified by extraneous factors (study design, duration of treatment, life expectancy, tumor type, and chemotherapy type); and 3) estimates adjusted for differences among studies in demographics, clinical patient characteristics, or study design characteristics.

Each study arm contributed a cohort to the overall analyses. Therefore, a study with two epoetin alfa doses and a control group contributed three cohorts. Some heterogeneity in study design was encountered. Both single-arm and controlled trials were included, as noted above. Some of the controlled trials used a placebo control arm, whereas others used a no-treatment control arm. Both are treated as control cohorts in this metaanalysis.

Baseline demographics, clinical characteristics, and QOL were analyzed for epoetin alfa patients and control patients. Data on whether patients were receiving chemotherapy at the time of study entry were available at the cohort level rather than the patient level. The mean scores, 95% confidence intervals, and *P* values for homogeneity and publication bias were calculated.

The unadjusted changes in the mean QOL scores from prestudy testing to on-study testing was calculated for epoetin alfa patients and control patients. Like the baseline data, the mean scores, 95% confidence intervals, and *P* values for homogeneity and publication bias were calculated. Stratified analyses were then conducted to examine the effects of study design, duration of treatment, life expectancy, tumor stratum, and chemotherapy type on the mean QOL changes. Subsequently, two analyses were performed to assess the extent to which any changes in QOL were attributable to epoetin alfa. First, the response changes were adjusted for several potentially confounding factors (age, gender, baseline scores, study design, and duration of therapy) using regression analysis. Second, in a separate analysis, the QOL response to epoetin alfa therapy was adjusted *directly* to eliminate the placebo effect by subtracting the control response from the active therapy response in each study. The placebo (control) arms used in the analysis of placebo effect were drawn from any study that contained a nontreatment group, regardless of its experimental design.

Statistics

Imputed variance.

Combined estimates were calculated when three or more cohorts were available. Simple combined estimates were formed using the DerSimonian and Laird approach.[34] In very few instances, estimates of baseline mean or mean QOL responses were obtained without corresponding estimates of variance (standard deviation [SD] or standard error). In these instances, an SD was imputed from the mean of the known SDs. In a number of cases, the response data available were the mean and variance in a prestudy condition and after therapy. The within-patient variance in these cases could not be calculated directly and was approximated by assuming independence (i.e., variances were calculated, although two independent samples were involved).

Controlling for bias.

Controlling for potentially biasing factors was carried out both by stratification and by statistical modeling. Statistical models of metaregression were used as an adjunct to controlling for the potentially biasing effects of extraneous factors. A number of potentially confounding factors were chosen that were both relevant, a priori, and generally available from the reports obtained. The following potentially confounding factors were analyzed statistically: study design (RCT vs. other), mean age, gender, tumor stratum (solid vs. mixed or hematologic malignancy), duration of therapy (8–12 weeks vs. 16–30 weeks), and baseline mean of QOL parameter.

Between-study homogeneity.

The extent to which studies yielded homogeneous estimates of response to therapy was assessed using the Cochrane test.[34]

Analysis of publication bias.

Analysis of publication bias was undertaken using the test described by Egger et al.[35] The statistical test amounts to a nonparametric correlation of standardized effect size estimates correlated with their variances.

RESULTS

Overview of the Evidence Base

Based on a systematic data base search and literature review, 23 clinical trials that enrolled 11,459 patients were identified that fit the criteria for inclusion in this metaanalysis (Table 1). Each study arm was analyzed as a separate cohort, so that a single study could contribute multiple cohorts. Table 2 provides an overview of study characteristics for epoetin alfa cohorts and control cohorts. The distribution of tumor strata and duration of therapy did not differ markedly between the two groups. The majority of cohorts derived from studies in which all patients were receiving chemotherapy (79% of epoetin alfa cohorts and 77% of control cohorts). Note that, by definition, control cohorts could be drawn only from RCTs, whereas epoetin alfa cohorts were drawn from both RCTs and single-arm studies.

Overall, baseline demographic and clinical characteristics for epoetin alfa-treated and control patients were similar (Table 3). The percentage of females in the control group was slightly greater compared with percentage of females in the epoetin alfa group, but the difference was not statistically significant. This slight difference may have been due, in part, to the fact that the 3 large, community-based studies,[26–28] which contributed 67% of patients to the metaanalysis, included lower proportions of females than most of the trials. Table 3 also reports the baseline mean QOL scores for both treatment groups. Note that where it is indicated that data were not available, it is possible that either that no data were reported or that fewer than three cohorts reported this factor. Although they did not differ significantly, mean baseline CLAS and FACT scores (with the exception of the FACT-An Total) were consistently lower for epoetin alfa-treated patients compared with control patients (Table 3). The FACT-An subscale score was > 6 points lower for the epoetin alfa-treated patients at baseline compared with the control patients. These scores were influenced heavily by the three community-based studies, which had patients with lower QOL scores at study entry.[26–28] Twenty studies reported baseline ECOG scores that were similar in epoetin alfa-treated and control patients. The SF-36 scores also were included in the metaanalysis, even though only three studies (Littlewood et al.[7] and unpublished data) contributed SF-36 subscale data. The baseline SF-36 scores were nearly identical (Table 3).

Many of the baseline mean values showed statistically significant heterogeneity in the results for both the epoetin alfa-treated and control cohorts (Table 3). Tests of publication bias for baseline conditions were conflicting. There was little evidence of publication bias in control cohort baseline results, but there were scattered suggestions of bias in epoetin alfa cohort baseline results.

Effect of Epoetin Alfa Treatment on QOL Mean Change Scores

Overview of effect.

The metaanalysis of the 23 trials showed a clinically and statistically significant beneficial effect of epoetin alfa in improving the QOL of patients according to a number of scales (sample sizes are provided in Table 4). Most of the subscales analyzed showed that QOL scores improved for patients who received epoetin alfa but not for control patients (Table 5). The most definitive results were seen in the cancer-specific subscales focused on anemia (Energy and Vitality). When the large studies by Glaspy et al.,[26] Demetri et al.,[27] and Gabrilove et al.[28] were removed, the improvement in QOL scores remained statistically significant. When QOL scores were adjusted for confounding factors and placebo effects, the results remained statistically significant ($P < 0.05$).

Unadjusted QOL subscale mean change scores.

There was a clear and positive improvement in the mean change from baseline scores for the three CLAS subscales in epoetin alfa–treated patients (Fig. 1). The improvement from baseline was significant ($P < 0.05$) and substantial (20–25%) (Table 5). Similarly, the epoetin alfa-treated patients experienced statistically significant improvements ($P < 0.05$) in the mean change from baseline scores for the FACT subscales, whereas the scores for control patients remained unchanged or worsened (Fig. 2). The biggest FACT subscale changes in the epoetin alfa-treated patients were in the FACT-F (17%) and the FACT-An (12%). The ECOG mean change scores did not differ significantly for epoetin alfa-treated patients. However, the control patients worsened significantly ($P < 0.05$) on this scale (an increase represents decreased QOL). Four SF-36 subscales (Physical Function, Role Physical, Vitality, and Social Function) improved significantly in the epoetin alfa patients ($P < 0.05$).

There was significant heterogeneity in the QOL mean change scores for many of the epoetin alfa QOL subscales and for some of the control group QOL subscales. There was no suggestion of publication bias in the estimates of response in QOL in either epoetin alfa cohorts or control cohorts. This stands in contrast to the earlier finding of some suggestion of bias in epoetin alfa baseline results. Because the response to therapy is the key outcome, the bias in the baseline

TABLE 1
Study Characteristics and Enrollment Data for the 23 Included Studies

Study identification[a]	Study design	Double-blind?	QOL measures used	No. of patients enrolled	Percentage of total patients enrolled	Tumor stratum	Tumor stratum: specification
Ward H87-032, 87-014, 87-015[b]	RCT	Yes	CLAS, ECOG	24	1.1	Mixed	NA
Case et al, 1993[37]	RCT	Yes	CLAS, ECOG	157	1.4	Mixed	Excluding acute leukemias and myeloid malignancies
Ludwig et al., 1993[38]	OL	No	ECOG	67	0.6	Mixed	NA
Ludwig et al., 1993[38]	OL	No	ECOG	34	0.3	Mixed	Multiple myeloma; squamous cell carcinoma
Henry et al., 1995[40]	RCT	Yes	CLAS, ECOG	132	1.2	Mixed	Excluding acute leukemias and myeloid malignancies
Glaspy et al., 1997[26]	OL	No	CLAS, ECOG	2342	20.4	Mixed	Nonmyeloid malignancies
Pawlicki et al., 1997[42]	OL	No	CLAS	215	1.9	Mixed	NA
Demetri et al., 1998[27]	OL	No	CLAS, FACT-An, FACT-An Total	2370	20.7	Mixed	Nonmyeloid malignancies
EPO-INT-27, 1998[c]	OL	No	CLAS, FACT-G, FACT-F, FACT-An, FACT-An Total, ECOG	39	0.3	Solid	NA
EPO-INT-3, 1999[c]	RCT	Yes	ECOG	201	1.8	Mixed	NA
J89-040, 1999[c]	RCT	Yes	CLAS, ECOG, SF-36 (8 items)	221	1.9	Hem	Chronic lymphocytic leukemia
RWJ 22512, 1999[c]	RCT	Yes	CLAS, ECOG, SF-36 (8 items)	45	0.4	Hem	Chronic lymphocytic leukemia
Thatcher et al., 1999[43]	RCT	No	CLAS, ECOG	130	1.1	Solid	Small cell lung carcinoma
Davies, 2000[44]	RCT	No	CLAS, FACT-An Total, ECOG, NHP (6 items)	120	1.0	Solid	NA
Dammacco et al., 2001[44]	RCT	Yes	CLAS, ECOG, NHP (6 items)	145	1.3	Hem	Multiple myeloma
EPO-INT-22, 2001[c]	RCT	No	ECOG	368	3.2	Solid	NA
Gabrilove et al., 2001[28]	OL	No	CLAS, FACT-F, FACT-An, ECOG	3012	26.3	Mixed	Nonmyeloid malignancy
Littlewood et al., 2001[7]	RCT	Yes	CLAS, FACT-G, FACT-F, FACT-An, FACT-An, Total, ECOG, SF-36 (8 items)	375	3.3	Mixed	Solid or nonmyeloid hematologic malignancy
McAdams, 2001[c]	RCT	No	FACT-An Total, ECOG	95	0.8	Solid	NA
Quirt et al., 2001[45]	OL	No	CLAS, FACT-G, FACT-F, FACT-An, FACT-An Total, ECOG	401	3.5	Mixed	Nonmyeloid malignancy
Wilkinson et al., 2001[46]	RCT	No	CLAS, FACT-F, FACT-An Total, ECOG	182	1.6	Solid	Ovarian
Chang and Couture, 2003[47]	RCT	No	CLAS, FACT-F, FACT-An	138	1.2	Solid	NA
Granetto et al., 2003[48]	RCT	No	CLAS, ECOG	546	4.8	Mixed	NA

QOL: quality of life; RCT: randomized controlled trial; CLAS: Cancer Linear Analog Scale; ECOG: Eastern Cooperative Oncology Group scale; NA: not available; OL: open label; FACT: Functional Assessment of Cancer Therapy scale; FACT-An: FACT Anemia Subscale; unpub data: unpublished data; FACT-G: FACT General Scale; Hem: hematologic; NHP: Nottingham Health Profile; SF-36: Short-Form 36-item scale.

[a] Data on 874 patients (7.6%) were obtained from a total of 6 unpublished studies.

[b] Data on patients from this study are also reported in Abels, 1992[24,25]; Case et al., 1993[36]; and Abels et al., 1996.[41]

[c] Unpublished data.

TABLE 2
Overview of Included Studies

Feature	No. of cohorts (%)		*P* value
	Epoetin Alfa	Control	
Total cohorts included in analysis	28	13	—
RCT design	18 (64)	13 (100)	—
Double-blind	8 (29)	8 (62)	0.04
Advanced disease	4 (50)	4 (100)	0.08
Baseline anemic[a]	25 (93)	12 (92)	> 0.9
Solid tumors	9 (32)	5 (38)	0.4
Mixed solid/hematologic tumors	16 (57)	5 (38)	0.4
Epoetin Alfa therapy for 8–12 weeks	12 (43)	8 (62)	0.3
Epoetin Alfa therapy for 16–30 weeks	16 (57)	5 (38)	0.3

RCT: randomized controlled trial.
[a] Definitions of anemia may vary among studies.

scores, although noteworthy, is not considered crucial.

Stratification analyses of unadjusted QOL mean change scores.

The mean change in QOL results was stratified by trial design. Improvements in CLAS data in the epoetin alfa group were statistically significant for both double-blind and open-label/single-arm studies ($P < 0.05$), with the biggest improvements seen in the open-label/single-arm studies.[26–28] This is because the 3 large, community-based studies demonstrated mean increases $\geq$ 10 points on each of these subscales, whereas the trials had a range of mean changes but a lower overall mean change for each of these scales. The other QOL scales were not stratified by trial design, because the distribution of designs used in the analyses for these scales was not varied.

The mean change in QOL results also was stratified by duration of epoetin alfa treatment. It is unlikely that QOL improves immediately with improved red blood cell production; hence, longer duration of therapy may be expected to produce greater responses in QOL. The studies that applied longer duration of epoetin alfa treatment tended to report larger increases in CLAS subscale scores, indicating that longer treatment with epoetin alfa brings about a cumulative increase in QOL. There was not enough FACT data for shorter studies to compare the response with longer studies. It is noteworthy that ECOG scores increased significantly for the longer studies ($P < 0.05$), representing a decline in performance status; whereas the increase remained statistically insignificant for the shorter studies. This indicates that there is a decrease in performance status over time in patients receiving chemotherapy for cancer.

The mean change in QOL results was stratified by life expectancy, because stage of disease was unavailable for half of the studies. This is considered potentially important, because chemotherapy may outweigh anemia therapy at some stages of some cancers. According to the change in CLAS scores, the patients in trials that selected participants with longer life expectancies experienced slightly greater increases in QOL. The FACT-An Total score increased significantly for the studies in patients with longer life expectancies ($P < 0.05$), whereas the increase was not statistically significant in the studies that included patients with shorter life expectancies. The ECOG scores did not change significantly in patients with shorter life expectancies, but ECOG scores increased (QOL deteriorated) significantly in studies that included patients with longer life expectancies ($P < 0.05$).

Stratification by tumor stratum also was conducted. The CLAS subscale scores improved significantly for both patients with solid tumors and patients with hematologic malignancies ($P < 0.05$). The FACT-An Total score improved to a statistically significant extent only in the studies that included hematologic malignancies ($P < 0.05$). The ECOG scores did not change significantly by tumor stratum.

The mean change in QOL scores also was stratified by chemotherapy type. Platinum-based versus nonplatinum-based chemotherapy agents often are discussed with regard to their differential impacts on QOL. Studies of patients who only received platinum-based chemotherapy did not have QOL results that differed substantively from the studies that included patients who received nonplatinum-based chemotherapy. However, the change in FACT-An Total score was statistically significant in the studies that included nonplatinum-based chemotherapy ($P < 0.05$), whereas the mean change scores for the platinum-only studies were positive but were not statistically significant.

Analysis for potentially confounding factors.

It was found that patients in the epoetin alfa cohorts and control cohorts generally were similar in terms of baseline characteristics. However, a combination of subtle differences between cohorts over a number of parameters cumulatively may lead to differences of some importance. Table 6 compares the QOL results after adjusting for a number of preselected factors (described above) with unadjusted results. The results of this analysis suggest that baseline factors did not confound the comparison of epoetin alfa cohorts and control cohorts. This was true of CLAS, FACT, and ECOG QOL measures. SF-36 results were not included in this analysis, because those data were noncancer-

TABLE 3
Included Patients' Baseline Demographics and Clinical Characteristics (n = 11,459)[a]

	Epoetin Alfa cohorts					Control cohorts				
				P value					*P* value	
Characteristic	Studies[b]	Value	95% CI	Heterogeneity	Bias	Studies[b]	Value	95% CI	Heterogeneity	Bias
Mean age (yrs)	7,24–28, 36,37,40–48[c]	59.6	58.3–60.8	< 0.001	0.004	7,24,25,36,37,40, 41,43,44,46,47[c]	61.1	58.4–63.9	< 0.001	0.8
Gender (%)										
Female	7,24–28, 36–48[c]	64.2	61.4–67.0	< 0.001	0.5	7,24,25,36,37,40, 41,43,46,47[c]	73.8	65.0–81.1	< 0.001	0.07
Male		35.8				26.2				
Disease duration (mos)	7,44,45,47[c]	30.0	20.2–39.8	< 0.001	0.006	7,43,44,47[c]	38.1	28.5–47.7	0.001	0.3
Hemoglobin concentration (g/dL)	7,26–28, 42–48[c]	9.9	9.7–10.2	< 0.001	0.03	7,43,44,46,47[c]	10.3	9.6–11.0	< 0.001	0.8
Hematocrit (%)	7,24–28,36, 37,40–44,48[c]	29.9	29.3–30.6	< 0.001	0.01	7,24,25,36,37, 40,41,43,44,46[c]	30.0	28.1–32.0	< 0.001	> 0.9
Derived hematocrit (%)	7,24–28,36, 37,40–48[c]	29.9	29.3–30.5	< 0.001	0.007	7,24,25,36,37, 40,41,43,44,46,47[c]	30.4	28.7–32.2	< 0.001	0.4
QOL scale										
CLAS										
Activity	7,268–28,37, 40,42,45–48[c]	44.7	42.9–46.6	< 0.001	0.001	7,24,25,36,37, 40,41,43,44,46,47[c]	48.2	44.08–52.3	< 0.001	0.5
Energy	7,26–28,37, 40,42,44,45–48[c]	43.7	42.0–45.4	< 0.001	0.001	7,24,25,36,37, 40,41,43,44,46,47[c]	47.0	42.6–51.4	< 0.001	0.3
Total QOL	7,26–28,37, 40,42,44,45–48[c]	48.9	47.4–50.4	< 0.001	0.009	7,24,25,36,37, 40,41,43,44,46,47[c]	52.9	49.3–56.6	< 0.001	0.7
FACT										
General	45,48[c]	73.7	69.8–77.7	< 0.001	0.6	—	NA	—	—	—
Fatigue	7,28,45–47[c]	26.7	24.8–28.6	< 0.001	0.2	7,46,47[c]	30.3	26.7–34.0	0.006	0.7
Anemia	7,27,28,45–47[c]	44.9	43.0–46.8	< 0.001	0.09	7,47	51.2	44.0–58.3	0.003	—
Anemia Total	7,27,45,46[c]	114.7	104.3–125.1	< 0.001	0.5	7,46[c]	113.1	90.3–135.8	< 0.001	0.4
ECOG	7,24–26,28,36–38,40, 41,43–46,48[c]	1.15	1.03–1.26	< 0.001	0.05	7,24,25,36,37, 40,41,43,44[c]	1.05	0.91–1.19	< 0.001	0.8
SF-36										
Physical Function	7[c]	52.8	5.0–55.7	0.8	0.01	7[c]	49.4	45.6–53.2	0.5	> 0.9
Role Physical	7[c]	28.5	24.3–32.6	0.3	0.4	7[c]	22.7	17.0–28.4	0.3	0.6
Pain	7[c]	69.4	62.4–76.3	0.01	0.7	7[c]	67.8	56.1–79.4	0.002	0.6
General Health	7[c]	40.9	34.2–47.6	0.005	0.06	7[c]	40.5	34.8–46.1	0.1	0.5
Vitality	7[c]	43.8	38.9–48.7	0.04	0.9	7[c]	44.7	39.5–49.8	0.1	0.1
Social Function	7[c]	62.6	59.7–65.5	0.7	0.2	7[c]	61.2	57.1–65.3	0.4	0.7
Role Emotion	7[c]	54.8	50.3–59.4	> 0.9	0.2	7[c]	54.5	37.9–71.0	0.002	0.7
Mental Health	7[c]	67.2	61.9–72.5	0.01	0.8	7[c]	63.9	55.6–72.3	0.003	0.8

95% CI: 95% confidence interval; QOL: quality of life; CLAS: Cancer Linear Analog Scale; FACT: Functional Assessment of Cancer Therapy scale; NA: not available; ECOG: Eastern Cooperative Oncology Group scale; SF-36: Short-Form 36-item scale.

[a] Note: Estimates are reported only for ≥ 3 cohorts.

[b] Numbers in the *Studies* columns correspond to numbers in the reference list.

[c] Unpublished data.

specific and were not as robust as the CLAS and FACT data: Only 3 of the studies that were included reported SF-36 results.

Analysis of placebo effects on QOL mean change scores. This analysis was conducted to estimate the degree of response of epoetin alfa-treated patients that is greater than can be accounted for by the placebo effect. These estimates were obtained by removing the control responses from the active therapy responses in each study that contained a nontreatment group, regardless of the study's experimental design. Subtracting the placebo response confirmed that the change in the CLAS subscales was substantial and statistically significant ($P < 0.05$). Similarly, the change in the FACT-F and FACT-An subscales also was statistically

TABLE 4
Accrued Patients in Each Treatment Group by Quality-of-Life Parameter (Unadjusted Response)

Parameter	Control cohort	Epoetin alfa cohort
CLAS Activity	568	7214
CLAS Energy	568	7185
CLAS Overall QOL	567	7212
FACT-An	139	4550
FACT-F	189	2910
FACT-G	88	503
FACT-An Total	208	2423
ECOG	623	7413
SF-36-Physical Performance	177	357
SF-36-Role Physical	176	356
SF-36-Physical Summary	86	179
SF-36-General Health	176	352
SF-36-Vitality	176	359
SF-36-Social Function	178	360
SF-36-Role Emotional	177	356
SF-36-Mental Health	176	359
NHP Emotion	119	150
NHP Energy	121	148
NHP Physical	120	149
NHP Sleep	121	150
NHP Social	118	150
NHP Pain	119	149
NHP Total	49	86

CLAS: Cancer Linear Analog Scale; FACT: Functional Assessment of Cancer Therapy scale; QOL: quality of life; ECOG: Eastern Cooperative Oncology Group scale; SF-36: Short-Form 36-item scale; NHP: Nottingham Health Profile.

significant ($P < 0.05$) after adjusting for placebo. However, the FACT-An Total change was not statistically significant, although the change was positive. ECOG scores did not change significantly after adjusting for placebo effects. Confirming the disease-specific and general QOL benefits seen in the CLAS and FACT results, all but 1 of the 8 SF-36 subscales changed in a positive direction, with 5 subscales (Physical Function, Role Physical, Vitality, Social Function, and Mental Health) showing statistically significant improvements ($P < 0.05$). The Physical Function, Role Function, and Vitality subscales are of particular interest, because these subscales would be expected, a priori, to improve with anemia correction.

There was no suggestion of publication bias in the placebo-adjusted estimates of response to therapy for any parameter. It also is important to note that, although the unadjusted estimates of QOL response exhibited substantial between-study variance, there was considerable homogeneity once placebo effects were removed. Thus, it appears that the effect of epoetin alfa is strong despite the heterogeneity in the sample populations.

DISCUSSION

In patients with cancer who are receiving chemotherapy, the impact of both the disease and the treatment can be severe. A common effect of cancer therapy is anemia, which is associated with a substantial decrease in patient QOL. The results of clinical trials have demonstrated that epoetin alfa corrects cancer-related anemia and significantly improves QOL in patients with cancer who are receiving chemotherapy.[7,27,28,49] The objective of the current metaanalysis was to evaluate the published and available unpublished data on the impact of epoetin alfa on QOL in patients with cancer who were or were not receiving chemotherapy.

The current study identified a significant positive effect of epoetin alfa on QOL, as measured with a variety of scales. There was a clear difference in QOL between epoetin alfa cohorts and control cohorts. It is noteworthy that the difference was most substantial in the QOL scales for which the effect of epoetin alfa would be expected a priori. In the CLAS Activity and Energy subscales, for example, the average responses for the epoetin alfa cohorts were 25% better than baseline scores, whereas the responses for the control cohorts were ± 3% compared with baseline responses. Similarly, epoetin alfa-treated cohorts improved by an average of 15% on the SF-36 Vitality subscale, compared with a 5% decrease for control cohorts. The results of the metaanalysis were upheld after adjusting for several confounding factors, indicating that epoetin alfa therapy has a direct effect on QOL in patients with cancer.

Although the effect of epoetin alfa was consistent across different studies, there was evidence of considerable variation between studies with respect to the magnitude of the response. This was evident in the significant heterogeneity for most QOL scales. The estimates of response in QOL parameters were largest in single-arm/open-label studies, which were dominated by three large, community-based studies that had among the largest estimates of the effect of epoetin alfa. The duration of epoetin alfa therapy also was an apparent factor. The degree of response increased with the length of the study and was associated with a greater increase in QOL. However, after adjusting for placebo effect, considerable homogeneity was seen in QOL response.

Stratification of mean QOL change results by life expectancy showed that, for FACT-An ($P < 0.05$) and possibly for CLAS, patients in trials that selected participants with longer life expectancies experienced greater increases in QOL. In contrast, ECOG scores showed QOL deterioration in studies that included

TABLE 5
Adjusted Mean Changes in Quality of Life Subscale Scores

	Epoetin Alfa cohorts					Control cohorts				
				P value					*P* value	
Subscale	Studies[a]	Score	95% CI	Heterogeneity	Bias	Studies[a]	Score	95% CI	Heterogeneity	Bias
CLAS										
Activity	7,26–28,37,40, 42,45,46,48[b]	10.3	8.8–11.8	< 0.001	0.2	7,24,25,36,37,40, 44–47[b]	−0.004	−2.6–2.6	0.3	0.3
Energy	7,26–28,37,40, 42,45,46,48[b]	10.4	8.7–12.0	< 0.001	0.06	7,24,25,36,37,40, 44–47[b]	1.4	−1.8–4.	0.03	0.5
Total QOL	7,26–28,37,40, 42,45,46,48[b]	9.0	7.3–10.7	< 0.001	0.5	7,24,25,36,37, 40,41,44–47[b]	−1.6	−4.1–0.9	0.2	0.06
FACT										
General	7,45[b]	3.2	2.0–4.3	0.6	0.8	—	NA	—	—	—
Fatigue	7,28,45–47[b]	4.6	4.2–5.1	0.5	0.3	7,46,47	−0.6	−3.5–2.2	0.01	0.4
Anemia	7,27,28,45,47[b]	5.3	4.4–6.1	0.08	0.4	1,11	−2.7	−4.8 to −0.6	> 0.9	—
Anemia Total	7,27,45,46[b]	7.3	4.7–9.8	< 0.001	0.9	7,45,46[b]	1.2	−2.5–5.0	0.008	0.5
ECOG	7,24–6,28,36–38, 40,41,43–46,48[b]	0.07	−0.02–0.16	< 0.001	0.001	7,24,25,36,37, 40,41,43,44,46[b]	0.18	0.02–0.34	0.002	0.9
SF-36										
Physical Function	7, 44[b]	3.5	0.6–6.5	0.6	0.9	7, 44[b]	−1.7	−5.7–2.2	0.5	0.5
Role Physical	7, 44[b]	11.0	6.3–15.7	0.8	0.1	7, 44[b]	3.2	−2.5–9.0	0.4	0.4
Pain	7, 44[b]	3.1	−0.3–6.4	0.4	> 0.9	7, 44[b]	1.4	−3.3–6.0	0.5	0.7
General Health	7, 44[b]	1.1	−2.6–4.8	0.3	0.2	7, 44[b]	−0.05	−5.1–5.0	0.3	0.4
Vitality	7, 44[b]	5.8	3.2–8.4	0.7	0.3	7, 44[b]	−2.5	−5.9–0.8	0.6	0.6
Social Function	7, 44[b]	5.0	1.6–8.5	> 0.9	0.7	7, 44[b]	−3.2	−8.6–2.2	0.4	0.3
Role Emotion	7, 44[b]	5.4	−0.2–11.0	0.7	0.3	7, 44[b]	5.9	−2.2–13.9	0.7	> 0.9
Mental Health	7, 44[b]	3.7	1.6–5.9	0.8	0.8	7, 44[b]	0.5	−2.4–3.4	0.6	0.4

95% CI: 95% confidence interval; CLAS: Cancer Linear Analog Scale; QOL: quality of life; FACT: Functional Assessment of Cancer Therapy scale; NA: not available; ECOG: Eastern Cooperative Oncology Group scale; SF-36: Short-Form 36-item scale.

[a] Numbers in the *Studies* columns correspond to numbers in the reference list.

[b] Unpublished data.

patients with longer life expectancies ($P < 0.05$). Patients who are at the end stage of their disease generally will have the greatest deterioration in their QOL and, thus, also have the greatest capacity to improve their QOL scores. Because CLAS and other QOL scales measure overall physical and mental well being, there is a greater potential for patients to improve these scores. However, ECOG measures only physical well being, and patients at the end stage of cancer have little capacity to improve physically. In contrast to the FACT-F scale, any improvements in fatigue are not expected to be detected by ECOG. In addition, in contrast to the CLAS, FACT, and SF-36 instruments, which are self-reported by patients, the ECOG/WHO scale is recorded by clinicians. Studies have shown that physicians and patients differ in their perceptions of the extent to which anemia-associated symptoms, such as fatigue, adversely affect patients' daily lives.[10] Therefore, due to physician reporting, ECOG-derived and WHO-derived data may understate somewhat the difference between cohorts receiving epoetin alfa treatment and untreated cohorts.

There was no clear evidence of publication bias, suggesting that the results represent a reasonable view of the evidence available. However, it is noteworthy that the quantity of data available varied substantially for different QOL scales. Hence, the depth of data used to draw conclusions is variable but apparently unbiased.

Despite some variations in statistical significance, the results of this metaanalysis show that epoetin alfa significantly improves QOL for patients with cancer, irrespective of chemotherapy use. Specifically, epoetin alfa significantly improved QOL using scales that focus

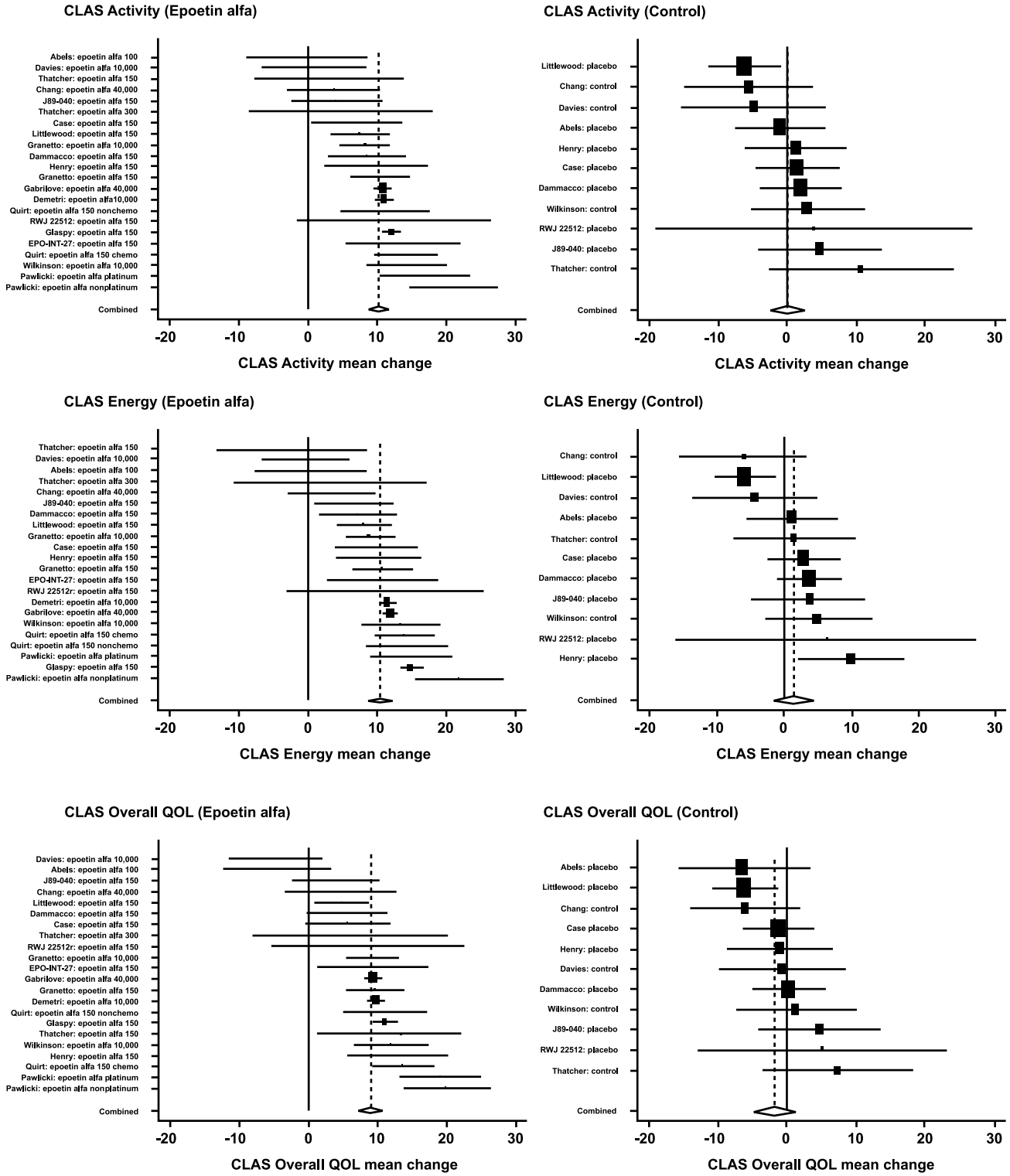

FIGURE 1. Comparison of mean changes in unadjusted Cancer Linear Analog Scale (CLAS) quality-of-life (QOL) scores for epoetin alfa cohort and control cohort. The point labeled "combined" represents the pooled estimate of response for each product. The center of the diamond represents the pooled estimate, whereas the extremities of the diamond represent the boundaries of the 95% confidence interval. Both were estimated under the random-effects model. nonchemo: nonchemotherapeutic regimen; chemo: chemotherapeutic regimen; platinum: platinum-containing regimen; nonplatinum; nonplatinum-containing regimen.

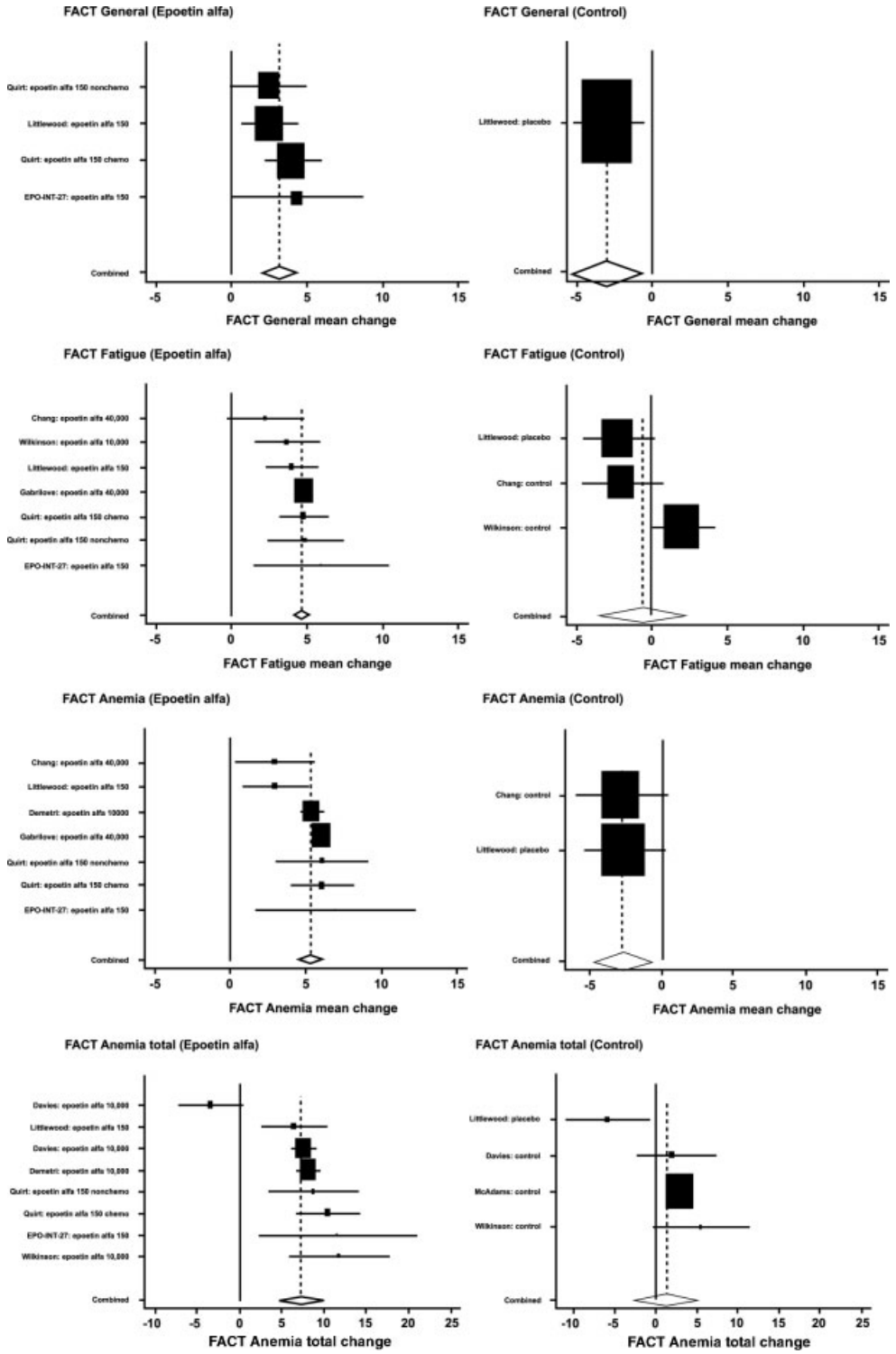

FIGURE 2. Comparison of mean changes in unadjusted Functional Assessment of Cancer Therapy (FACT) quality-of-life (QOL) scores for epoetin alfa cohort and control cohort. The point labeled "combined" represents the pooled estimate of response for each product. The center of the diamond represents the pooled estimate, whereas the extremities of the diamond represent the boundaries of the 95% confidence interval: Both were estimated under the random-effects model. nonchemo: nonchemotherapeutic regimen; chemo: chemotherapeutic regimen.

TABLE 6
Adjusted Estimates of Differences in Mean Quality-of-Life Change Scores from Baseline (Epoetin Alfa vs. control)

		Unadjusted difference (95% CI)		
QOL measure	Adjusted difference (95% CI)	Age and gender	Age, gender, and baseline score	Age, gender, baseline score, trial design (RCT vs. other), and duration of epoetin alfa therapy (16–30 weeks vs. 8–12 weeks)
CLAS				
Activity	9.9 (6.4–13.5)	9.5 (5.9–13.1)	8.5 (5.2–11.8)	7.3 (4.3–10.3)
Energy Levels	8.7 (4.8–12.6)	8.4 (4.4–12.5)	6.9 (3.2–10.7)	5.8 (2.3–9.3)
Overall QOL	1.0 (6.0–14.0)	9.3 (5.5–13.1)	7.7 (4.1–11.3)	7.7 (5.1–10.4)
FACT Total	6.2 (0.6–11.7)	6.5 (−0.2–13.1)	5.4 (3.4–7.3)	4.2 (2.1–6.4)
ECOG	−0.1 (−0.3–0.1)	−0.1 (−0.3–0.1)	−0.1 (−0.3–0.1)	−0.1 (−0.3–0.0)

95% CI: 95% confidence interval; QOL: quality of life; RCT: randomized controlled trial; CLAS: Cancer Linear Analog Scale; FACT: Functional Assessment of Cancer Therapy scale; ECOG: Eastern Cooperative Oncology Group scale.

on cancer and anemia. With the exception of the FACT-An Total, all FACT subscales (FACT-G, FACT-F, and FACT-An), as well as the CLAS subscales for Energy and Activity and the SF-36 Vitality subscales, showed substantial improvement for epoetin alfa-treated patients, but not for control patients. When the data were adjusted for confounding factors and placebo effect, the epoetin alfa-treated cohorts continued to show significant improvements in QOL. Based on these comprehensive results, epoetin alfa is an effective therapy that improves QOL for patients with cancer.

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