# Weekly Erythropoietin Improves Anemia Associated with Cancer Treatment

*Witzig TE, Silberstein PT, Loprinzi CL, et al. Phase III, randomized, double-blind study of epoetin alfa versus placebo in anemic patients with cancer undergoing chemotherapy. J Clin Oncol 2004;0:200410020.*

## Study Overview

Objective. To determine whether weekly epoetin alfa improves hemoglobin (HgB) levels, reduces red blood cell transfusions, and improves quality of life (QOL) in patients with advanced cancer and anemia after receiving myelosuppressive chemotherapy.

Design. Randomized, double-blind, placebo-controlled trial.

Setting and participants. Patients with metastatic cancer receiving myelosuppressive treatment were randomized to receive placebo or subcutaneous epoetin alfa (Ortho Biotech, Bridgewater, NJ) 40,000 U weekly for 16 weeks. Eligible patients had anemia (males, HgB < 11.5 g/dL; females, HgB < 10.5 g/dL) and a normal or elevated ferritin level. Patients with anemia secondary to vitamin deficiency ($B_{12}$, folic acid, or iron), gastrointestinal blood loss, or hemolysis were not eligible. Patients were instructed to take oral ferrous sulfate 324 mg/day. After the first month, the dose of epoetin alfa was increased to 60,000 U weekly if the HgB level had not increased by more than 1.0 g/dL or if the patient had required a transfusion. Patients received red blood cell transfusions at the discretion of the treating physician. If the HgB level increased to more than 15 g/dL, complete blood count was to be repeated 1 week later. If the HgB level remained higher than 15 g/dL, epoetin alfa was discontinued until the HgB was less than 13.0 g/dL and then restarted at 75% of the prior dose.

Main outcome measures. Scores for QOL obtained at random assignment and monthly during treatment (Uniscale, SDS, and FACT–An). Secondary endpoints were the proportion of patients who required transfusions, the average change in HgB levels from baseline (HgB response), and the incidence of HgB levels lower than 9.0 g/dL.

Main results. 344 patients were randomized. The 2 treatment groups were similar with respect to baseline characteristics (HgB, ferritin level, type of chemotherapy and dose intensity, tumor objective response rate, stable disease, and progression). Placebo-treated patients had a mean HgB increase of 0.9 g/dL (range, 3.8–5.3) compared with 2.8 g/dL (range, 2.2–7.5) for epoetin-treated patients ($P < 0.001$). During the study, 32% of placebo-treated patients achieved a 2–g/dL HgB increase as compared with 73% of epoetin-treated patients ($P < 0.001$). The incidence of red blood cell transfusion for placebo and epoetin treatment arms was 40% and 25% ($P = 0.005$), respectively. The placebo group received 256 U of red blood cells compared with 127 U in the epoetin group ($P < 0.001$). The average change in HgB showed equivalent response to epoetin alfa among the main primary malignant disease types. The incidence of toxicity in the groups was similar, and there were no differences in overall survival. Changes in the average QOL scores from baseline to the end of the study were similar in the 2 groups. The HgB responders (irrespective of treatment arm) had a mean change in Functional Assessment of Cancer Therapy fatigue score from baseline of 5.1 compared with 2.1 for the nonresponders ($P = 0.006$).

Conclusion. Epoetin alfa significantly improved HgB levels and reduced transfusions in patients with advanced cancer and anemia after receiving myelosuppressive chemotherapy.

## Commentary

Anemia is a significant and common toxicity associated with systemic chemotherapy. Anemia contributes to fatigue, hypotension, cardiotoxicity, dyspnea, renal insufficiency, and cold intolerance. Persistent anemia also may delay or alter subsequent chemotherapy scheduling, potentially compromising treatment efficacy.

Recombinant erythropoietin is a colony-stimulating factor approved for the treatment of anemia due to chemotherapy

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for nonmyeloid cancers. A recent meta-analysis of over 30 trials concluded that erythropoietin reduces transfusion requirements [1]. Additionally, emerging evidence suggests increased HgB levels due to erythropoietin correlates with improvements in QOL [2]. The approved initial dosing of erythropoietin is 150 U/kg subcutaneously 3 times/week. However, this inconvenient scheduling has been largely supplanted in community and academic centers by weekly dosing at 40,000 U, albeit in the absence of prospective data.

In the current study, Witzig et al report the first randomized, placebo-controlled trial of weekly erythropoietin. Weekly dosing resulted in expected improvements in HgB levels and in reducing transfusion requirements as compared with placebo. Indeed, these data are comparable to findings seen in 3 times/week dosing. However, the study's primary objective, improvement in QOL, was not met, although a subset analysis found an improvement in fatigue for patients receiving erythropoietin. One possible explanation for the lack of improvement in overall QOL was that the placebo group had a higher baseline QOL score than the treatment group, making it more difficult to demonstrate a difference between groups with treatment. Additionally, as the authors point out, the increased rate of transfusions in the placebo group may have negated impairments in QOL due to anemia. Previous trials demonstrating improvements in QOL (with 3 times/week scheduling) were often open-label, single-cohort, uncontrolled trials. Witzig et al's trial raises the question of erythropoietin's widely perceived (and advertised) value in improving global QOL for patients with cancer. Finally, this was not a trial comparing weekly erythropoietin dosing with 3 times/weeks dosing; this is a clinical question that remains unanswered.

## Applications for Clinical Practice

Weekly scheduling of recombinant erythropoietin appears to be effective in improving anemia and reducing red blood cell transfusions in patients with cancer receiving myelosuppressive chemotherapy. Other causes of anemia, especially iron deficiency, need to be appropriately addressed before initiating erythropoietin therapy.

*–Review by David R. Spigel, MD*

## References

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