

Clinical benefits and risks associated with epoetin (alfa/beta) and darbepoetin alfa in patients with chemotherapy-induced anemia: a systematic review of the literature

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Origin of Study	USA
Type of Study	SYSTEMATIC LITERATURE REVIEW
Objectives	Assess the clinical efficacy, safety, and effectiveness of epoetin alfa (Procrit) and darbepoetin alfa (Aranesp) in treating chemotherapy-induced anemia (baseline hemoglobin level < 11 g/dL).
Study Design	In all, 28 controlled trials of epoetin alfa and 6 prospective uncontrolled trials of ≥ 300 chemotherapy-induced anemia patients were systematically reviewed. Investigators performed meta-analyses of transfusions, venous thromboembolism, Functional Assessment of Cancer Therapy–Fatigue (FACT–F) results, and on-study deaths.
Patients	In all, 8,323 patients participated in controlled trials of epoetin alfa, including 10 that compared the drug with darbepoetin alfa; 9,971 patients participated in 6 uncontrolled trials. Further, there were 4 controlled trials involving darbepoetin alfa ($n = 984$) that did not include the comparative trials previously mentioned in addition to 2 uncontrolled studies ($n = 2,300$).
Observations	The odds ratio (OR [95% confidence interval]) for transfusions in the epoetin alfa versus control trials was 0.44 (0.35, 0.55, respectively), in the darbepoetin alfa versus control trials was 0.41 (0.31, 0.55), and in the epoetin alfa versus darbepoetin alfa trials was 0.77 (0.58, 1.02). Meta-regressions did not identify significant predictors of transfusions. The mean change in score for FACT–F in the epoetin alfa versus control trials was +3.40 versus –0.53 and in the darbepoetin alfa versus control trials was +4.50 versus –1.67. The frequency of venous thromboembolism in the epoetin alfa versus control trials was 4.3% versus 1.9% (OR 1.97 [0.77, 5.04]) and in the darbepoetin alfa versus control trials was 4.4% versus 3.1% (OR 1.44 [0.27, 2.61]). One epoetin alfa versus darbepoetin alfa trial reported venous thromboembolism at 7.0% versus 5.9%, respectively (OR 1.19 [0.72, 1.65]). On-study deaths in the epoetin alfa versus control trials was 10.3% versus 10.6% (OR 0.86 [0.58, 1.28]) and in the darbepoetin alfa versus control trials was 7.3% versus 6.8% (OR 1.26 [0.74, 2.14]). Just one epoetin alfa versus darbepoetin alfa trial reported on-study deaths at 12.9% versus 15.6% (OR 0.81 [0.21, 1.40]). For most outcomes, effectiveness and safety results from community studies did not differ substantively from those found in clinical trials.
Conclusions	A systematic review of current best evidence on erythropoietins showed these drugs to be safe and effective in treating chemotherapy-induced anemia and its symptoms, leading to improvement in fatigue levels.
Discussion	For patients with chemotherapy-induced anemia, evidence-based guidelines recommend maintaining hemoglobin levels between 11 and 13 g/dL by treating with erythropoiesis-stimulating agents. However, most guidelines do not yet include darbepoetin alfa, nor do recent reviews quantify quality-of-life outcomes. Furthermore, outcomes are unknown regarding the impact of recent changes in the product

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labels regarding the risk of venous thromboembolism. To address these evidence gaps, these investigators conducted a systematic review of the literature, which contains what is recognized as the current best evidence on the topic.

The meta-analysis showed that patients who received erythropoiesis-stimulating agents required fewer transfusions. The OR for transfusions in patients receiving epoetin alfa, versus controls, was 0.44; for darbepoetin alfa versus controls, the OR was 0.41. The OR for epoetin alfa versus darbepoetin alfa was 0.77, which was not statistically significant. Regression analyses failed to identify any significant predictors of the need for transfusions.

With the FACT-F instrument for assessment, patients in the studies who received erythropoiesis-stimulating agents had improvements in fatigue. Mean fatigue scores improved by over 3 points with epoetin alfa and declined a half point in controls; scores improved by 4.5 points with darbepoetin alfa and declined over 1.5 points in those studies' control subjects.

A slight increase in venous thromboembolism was reported for the erythropoiesis-stimulating arms in these studies. "According to the numbers, these agents display a higher risk for venous thromboembolism than controls, and in the one study comparing epoetin alfa to darbepoetin alfa, the risk was higher for epoetin alfa," said co-author Dr. Sercus. "The results were neither statistically nor clinically significant, so all we can really say is that it 'looks' like people on erythropoiesis-stimulating agents are at greater risk for venous thromboembolism."

On-death study rates, however, were about 10% in both arms in studies comparing epoetin alfa and controls, and about 7% in both arms of studies evaluating darbepoetin alfa and controls. Only one study reported on-study deaths comparing epoetin alfa and darbepoetin alfa and found these rates to be 12.9% and 15.6%, respectively.

For most of the outcomes, the efficacy and safety of these agents were similar between community studies and clinical trials, suggesting that the good results seen in clinical trials of these agents are translated into actual clinical practice. "However, randomized controlled trials are known to have low external validity, ie, low transferability of findings to real-world settings, which requires large trials or prospective observational studies to assess," Dr. Ross noted.

This review demonstrates that chemotherapy-related anemia is effectively treated with either of these agents. There were no clinically important differences between the two agents, suggesting that clinicians have two good options for treating chemotherapy-induced anemia.

Key Points

- No clinically important differences between these erythropoietins were found.

Reference

Ross SD, Allen IE, Henry D, Seaman C, Sercus B, Goodnough LT. Clinical benefits and risks associated with epoetin (alfa/beta) and darbepoetin alfa in patients with chemotherapy-induced anemia: a systematic review of the literature. Presented at the 18th Annual Symposium of the Multinational Association of Supportive Care in Cancer; June 22–24, 2006; Toronto, Canada. Abstract 02-006.