Review: Erythropoietin or darbepoetin for anemia in patients with cancer produces both benefits and harms with no increase in survival

Bohlius J, Wilson J, Seidenfeld J, et al. **Erythropoietin or darbepoetin for patients with cancer.** Cochrane Database Syst Rev. 2006;(3):CD003407.

Clinical impact ratings: Hematol/Thrombo ★★★★★☆☆ Oncology ★★★★★☆☆

QUESTION

In patients with cancer, are erythropoietin and darbepoetin effective and safe for prevention or treatment of anemia?

METHODS

Data sources: MEDLINE (to April 2005), Cochrane Central Register of Controlled Trials, EMBASE/Excerpta Medica, Science Citation Index (to September 2004), conference abstracts (to December 2004), reference lists, experts in the field, drug companies, and the U.S. Food and Drug Administration Web site.

Study selection and assessment: Randomized controlled trials (RCTs) with ≥ 10 patients per group that compared recombinant human erythropoietin or darbepoetin, given subcutaneously or intravenously at doses ≥ 300 U/kg per week (no minimum dose restriction for darbepoetin) for ≥ 4 weeks, with placebo or no treatment (concomitant cancer or supportive treatments were allowed as long as they were balanced between the groups) for prevention or treatment of anemia in patients of all ages with cancer. 57 RCTs (n = 9353) met the selection criteria. Methodological quality was assessed based on randomization method, concealment of allocation, blinding, follow-up, and intention-to-treat analysis.

Outcomes: Red blood cell transfusion, hematologic response (in patients with anemia, defined as an increase in hemoglobin [Hb] level ≥ 2 g/dL or in hematocrit ≥ 6 percentage points), survival, complete tumor response, quality of life, complications, increase in Hb levels, and number of red blood cell units transfused.

MAIN RESULTS

Treatment with erythropoietin or darbepoetin was associated with decreased need for red blood cell transfusion, increased rate of hematologic response, and increased risks for thromboembolic events and hypertension (Table). Groups did not differ for complete tumor response or survival (Table). Hb levels increased by a mean 1.8 g/dL (95% CI 1.7 to 1.9) more in the intervention group than in the control group (15 RCTs, n = 2697), and the number of red blood cell units transfused was lower by a mean 1.1 units (CI 0.8 to 1.3) (14 RCTs, n = 2353). Effects were similar for the 2 types of drug. Evidence from 16 RCTs (n = 3670) suggests that erythropoietin and darbepoetin may improve quality of life.

CONCLUSION

In patients with cancer, erythropoietin and darbepoetin are effective for prevention or treatment of anemia but are associated with increased risk for thromboembolic events and do not increase survival.

Sources of funding: Department of Health UK; University of Birmingham, Department of Public Health and Epidemiology UK; German Ministry of Education and Research.

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Erythropoietin or darbepoetin (intervention) vs placebo or no treatment (control) for prevention or treatment of anemia in patients with cancer*

Outcomes	Number of trials (n)	Weighted event rates		RRR (95% CI)	NNT (CI)
		Intervention	Control		
Red blood cell transfusion	42 (6510)	31%	48%	36% (32 to 40)	6 (6 to 7)
				RBI (CI)	NNT (CI)
Hematologic response	22 (4307)	54%	16%	243% (207 to 284)	3 (3 to 4)
Complete tumor response	13 (2833)	27%	24%	9% (–6 to 26)†	Not significant
				RRI (CI)	NNH (CI)
Venous thromboembolism	35 (6769)	6.5%	3.9%	67% (35 to 106)	39 (25 to 74)
Hypertension	16 (2263)	9.1%	7.4%	24% (0 to 54)	57 (26 to ∞)
Death	42 (8167)	30%	29%	5.6% (0.7 to 12)‡	Not significant

*Abbreviations defined in Glossary; RRR, RBI, RRI, NNT, NNH, and CI calculated from relative risks and control event rates in article using a fixed-effects model.
†A random-effects model was used.
‡Calculated from odds ratio in article.

COMMENTARY

The results of this well-done meta-analysis by Bohlius and colleagues are in keeping with current clinical guidelines. Erythropoietin is indicated for patients with cancer and anemia defined as an Hb level < 10 to 11 g/dL and for symptomatic patients with lesser degrees of anemia (1, 2). The goal of therapy is to improve the patient's quality of life and prevent transfusions. A target Hb level of 12 g/dL is recommended. All other causes of anemia should be excluded before initiating erythropoietin. Intravenous iron supplementation is a good strategy to ensure a response (68% vs 35% response rate with oral iron), although the optimal dose and frequency are not yet established (3). Prospective studies have not identified any useful predictors for response in patients with solid tumors (2).

Complications of erythropoietin include thromboemboli and hypertension that may be related to an Hb level > 12 g/dL. Recent research indicates that erythropoietin may adversely affect survival and disease progression in patients with tumors that express erythropoietin receptors (4).

When to start erythropoietin is a clinical judgment. It should be offered to symptomatic patients with moderate anemia. In asymptomatic patients with a slowly declining Hb level, erythropoietin may be considered. It is not indicated to improve survival or response to therapy.

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References

1. **Rizzo JD, Lichtin AE, Woolf SH, et al.** Blood. 2002;100;2303-20.
2. **Bokemeyer C, Aapro MS, Courdi A, et al.** Eur J Cancer. 2004;40:2201-6.
3. **Auerbach M, Ballard H, Trout JR, et al.** J Clin Oncol. 2004;22:1301-7.
4. **Henke M, Mattern D, Pepe M, et al.** SJ Clin Oncol. 2006;24:4708-13.