Venous thromboembolism and mortality associated with recombinant erythropoietin and darbepoetin administration for the treatment of cancer-associated anemia


CRD summary
This review, which assessed the safety of erythropoiesis-stimulating agents in cancer patients, concluded that they were associated with increased risk of venous thromboembolism and mortality. However, the absence of key study details means that the authors’ conclusions should be interpreted with caution.

Authors’ objectives
To evaluate venous thromboembolism (VTE) and mortality rates associated with the use of erythropoiesis-stimulating agents (ESAs) for treating anaemia in patients with cancer.

Searching
In addition to assessing the studies used in a previous Cochrane review (which covered the period 1 January 1985 to 1 April 2005; see Other Publications of Related Interest), the authors also searched MEDLINE and EMBASE from April 2005 to 17 January 2008; the search terms were reported. Searches were also made of the Food and Drug Administration website, presentations at the 2007 Oncology Drugs Advisory Committee meeting on ESAs, and phase 3 clinical trial summaries reported by health authorities, ESA manufacturers, or clinical investigators at national conferences.

Study selection
Phase 3 trials evaluating ESAs (versus placebo or standard care) for the treatment of anaemia in patients with cancer were eligible for inclusion.

Of the included studies, epoetin alpha or epoetin beta was used in 40 trials and darbepoetin was used in 11 trials. Where reported, the duration of treatment ranged from 6 to 52 weeks. The most common concomitant treatment was chemotherapy. Twenty-six trials included patients with cancer only at a specific site, the most common being lung cancer and breast cancer. The most common outcomes reported were treatment-related anaemia, survival and VTE.

The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
Outcome data were extracted and relative risks (RRs) or hazard ratios (HRs), along with 95% confidence intervals (CIs), were calculated. When mortality events were not available, HRs appear to have been estimated. When VTE events were not available, a correction factor (0.5) was used to calculate the RRs.

The reviewers independently extracted the data, with any disagreements resolved by one author not involved in the initial extraction.

Methods of synthesis
Meta-analyses examining pooled RRs or HRs were performed using a random-effects model. The studies appear to have been weighted using the inverse variance method. Subgroup analyses on clinical characteristics were also undertaken. Heterogeneity was assessed using the $\chi^2$ test and $I^2$ statistic.

Results of the review
Fifty-one trials (n=13,611) were included in the review. The sample sizes ranged from 30 to 985. The duration of
follow-up ranged from 11 to 62 months. Survival was examined in all 51 trials. Mortality was statistically significantly higher in the ESA group compared with the control group (HR 1.10, 95% CI: 1.01, 1.20, p=0.03). No significant heterogeneity was found between the 51 studies ($I^2=21.1\%$).

VTE was assessed for 38 trials (n=8,172). Patients taking an ESA were at a statistically significantly increased risk compared with the control group (RR 1.57, 95% CI: 1.31, 1.87).

Subgroup analyses examining mortality risk in groups who were, or were not, receiving chemotherapy or radiotherapy found a non significant increased risk in the ESA group (for anaemia of cancer and treatment-related anaemia subgroups).

**Authors' conclusions**
ESA administration to patients with cancer is associated with increased risks of VTE and mortality.

**CRD commentary**
The review addressed a clear question and was supported by appropriate inclusion criteria. Attempts to identify all relevant studies were undertaken by searching electronic databases and several other sources. The authors did not report whether their searches had any language restrictions, so it is difficult to comment on whether any relevant studies might have been missed. Although details of each study were provided, it was nevertheless unclear whether all studies were placebo-controlled and also what doses of ESA were used. The quality of the included studies was not assessed, making it very difficult to assess the strength of the evidence. Appropriate methods were used to pool the data and assess heterogeneity. The absence of any information on study quality, as well as other study details, means that the authors' conclusions, although reflecting the evidence presented, should be interpreted with caution.

**Implications of the review for practice and research**
Practice: The authors stated that their conclusions raise concern about ESA safety for patients with cancer.
Research: The authors stated that additional research on ESA safety is needed, and that future clinical trials should include the collection of tissue specimens to directly assess ESA effects in tumour cells.

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**Other publications of related interest**

This additional published commentary may also be of interest.

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.