The use of erythropoiesis-stimulating agents in patients with non-myeloid hematological malignancies: a systematic review
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CRD summary
The authors concluded that erythropoiesis-stimulating agents in patients with haematologic malignancies reduced transfusion requirements. Conclusions could be made for quality of life. Data were needed on effects on survival. The authors' conclusions reflect the evidence, but methodological limitations for some of the included studies and poor reporting of the review process should be borne in mind.

Authors' objectives
To assess the effectiveness of erythropoiesis-stimulating agents (ESAs) for treatment of anaemia in patients with non-myeloid haematological malignancies.

Searching
MEDLINE, EMBASE and The Cochrane Library were searched to March 2008 for English-language studies; search terms were reported.

Abstracts published in the proceedings of annual meetings of American Society of Clinical Oncology and the American Society of Hematology were searched from 1996 to 2007. Reference lists were searched manually.

Study selection
Randomised controlled trials (RCTs) that assessed either erythropoetin (epoetin alpha and beta) or ESAs (epoetin and darbepoetin) in patients with lymphoma, multiple myeloma, chronic lymphocytic leukemia and/or Hodgkin’s lymphoma were eligible for inclusion. Studies of patients with AIDS-associated lymphoma, patients with multiple myeloma with renal failure that required haemodialysis and patients who had peripheral blood stem cell transplantations were excluded. Primary outcome measures included survival, transfusion requirements, quality of life and correction/improvement of anaemia.

In the included studies, patient groups included those with: multiple myeloma only; solid tumours and non-myeloid haematological malignancies; multiple myeloma, lymphoma and chronic lymphocytic leukemia; diffuse large B cell lymphoma; and chronic lymphocytic leukemia. Most patients received chemotherapy at the time of treatment with erythropoietin; only one trial evaluated patients who did not receive chemotherapy. Most trials reported on use of erythropoietin. Four studies (three trials and one abstract) reported on use of darbepoetin alpha. Threshold haemoglobin concentration for transfusion ranged from 70g/L to 100g/L. Adverse events were reported. Assessment duration ranged from eight to 52 weeks.

Two reviewers independently selected studies for the review.

Assessment of study quality
Study quality was assessed based upon criteria of comparable groups, specified haemoglobin concentration for transfusion, blinded outcome assessment, confounding factors were considered, predetermined sample size, intention-to-treat analysis and adequate follow-up and handling of missing data.

The authors did not state how many reviewers performed the validity assessment.

Data extraction
Outcomes extracted were: increment in haemoglobin level; proportion of patients transfused; transfusion requirements; survival; quality of
life; and adverse events.

The authors did not state how data extraction was undertaken.

**Methods of synthesis**
Due to heterogeneity, studies were combined as a narrative synthesis and presented in tables. Numbers needed to treat (NNT) to prevent one transfusion or improve the quality of life in one patient were calculated for studies that showed a reduction in the proportion of patients transfused or an improvement in quality of life.

**Results of the review**
Nineteen studies (n=3,900 participants) were included in the review: 15 published trials and four abstracts. Seven trials and one abstract were double-blinded and placebo-controlled. Seven studies reported sample size calculations that were adequately powered. No studies were powered to detect a difference in survival and only one study was powered to detect a difference in quality of life. Six trials and three abstracts did not analyse their data based on intention-to-treat analysis. All fully published trials reported on the number of patients who completed the trials. Four publications had confounding and this could not be assessed for abstracts.

**Survival (five studies):** Two studies reported inferior survival in patients allocated to an ESA. Three studies failed to detect differences between groups.

**Quality of life (10 studies):** Four articles and three abstracts reported improvements in patients and three studies reported no improvements; methodological limitations were identified in these studies.

**Transfusions (nine studies):** Seven studies reported a statistically significant reduction in the proportion of patients transfused following therapy with ESAs. Reductions ranged from 15% to 40%. Five studies reported that erythropoietin/darbepoetin significantly decreased the proportion of patients transfused in patients with non-Hodgkin’s lymphoma, chronic lymphocytic leukemia and Hodgkin’s lymphoma. The absolute risk reduction in transfusions ranged from 15% to 24%. The number needed to treat to prevent a transfusion ranged from four to six.

**Change in haemoglobin/haematocrit:** Fifteen studies reported a statistically significant increase in haemoglobin concentration or haematocrit or in the proportion of patients with an increase in the haemoglobin concentration or haematocrit with use of erythropoiesis-stimulating agents.

**Adverse events:** There were no statistically significant differences in frequency of adverse events and mortality between erythropoietin and control groups (five studies). Four studies showed no statistically significant differences between darbepoetin and controls for adverse events or mortality.

**Authors’ conclusions**
Using erythropoiesis-stimulating agents in patients with haematologic malignancies reduced transfusion requirements. No definite conclusions could be made for quality of life. More data were needed on the effects on survival.

**CRD commentary**
The review question and supporting inclusion criteria were clearly stated. The literature search was limited to English-language articles, so language bias may have been introduced. Study quality was assessed using appropriate criteria and findings were reported. Study selection was done in duplicate, which reduced potential for reviewer error and bias; it was unclear whether this extended to data extraction and validity assessment. Few patient details were reported.

Given the variability among studies and (acknowledged by the authors) methodological limitations for the assessment of quality of life, a narrative synthesis was appropriate. The results were sometimes difficult to interpret as they appeared to be poorly or selectively reported. The results for survival were confusing as the authors reported findings from a systematic review and from two follow-up studies that did not meet their inclusion criteria.

The authors’ conclusions reflect the evidence, but methodological limitations and poor reporting of the review process should be borne in mind.
Implications of the review for practice and research

**Practice:** The authors stated criteria to be considered before using ESAs for a reduction in the proportion of patients transfused: the possibility of poorer survival, risk of thromboembolic events and tumour progression, individual patient values and the likelihood that a patient will require a transfusion.

**Research:** The authors stated that further data was needed on the effects of ESAs.

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