Uses of epoetin for anemia in oncology
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Authors' objectives
To assess the effectiveness of epoetin to prevent or correct mild to moderate anaemia related to cancer and cancer treatment.

Searching
The review included published evidence (including abstracts and articles in press). MEDLINE, EMBASE, and Cancerlit were searched from 1985 to 1998. The search terms used were given in the report. Issues of Current Contents and Medscape Oncology (to October 1999) and abstracts of the 1999 meeting of the American Society for Clinical Oncology were also searched, and the epoetin manufacturer Ortho Biotech was contacted. Reference lists from all identified articles, editorials and letters published from 1995 onwards were examined. No language restriction was imposed on the search and studies in languages other than English were actively sought through personal contact with researchers in the field.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) and non-randomised controlled trials were eligible for inclusion. Non-randomised studies that used concurrent or historical controls were included if the reviewers were able to determine that the groups were comparable. To be included, the studies had to have at least 10 patients in each group of interest (treatment, stratum, or epoetin dose level).

Specific interventions included in the review
Studies that compared the management of anaemia with and without the use of epoetin (recombinant human erythropoietin) were eligible for inclusion. In the included studies, epoetin with red blood cell (RBC) transfusion as necessary was compared with RBC transfusion alone; there were no trials comparing epoetin with other alternatives. Epoetin was given subcutaneously or intravenously.

Participants included in the review
The following were included.

1. Studies in cancer patients with, or at risk of, anaemia primarily due to conventional-dose chemotherapy and/or radiotherapy.

2. Studies in patients with anaemia due to cancer itself, who may or may not be receiving cancer therapy. To be included, the studies had to have ruled out at least one treatable cause of anaemia prior to enrolment. The patients in the included studies had multiple myeloma, non-Hodgkin's lymphoma, chronic lymphocytic leukaemia or myelodysplastic syndrome.

3. Studies in cancer patients with anaemia due to bone marrow ablation prior to stem cell transplantation, only if the data were reported separately for allogenic or autologous transplantation and use of peripheral blood or bone marrow stem cells. Participants in the included studies received bone marrow stem cells, except in one study of autologous transplantation where bone marrow and peripheral stem cells were used.

Adults and children were included. Studies in patients with malignant or nonmalignant conditions were included provided that less than 10% had nonmalignant conditions. Studies in patients undergoing surgery for cancer were excluded, as were studies of stem cell mobilisation.

Outcomes assessed in the review
Studies that reported any of the following outcomes were eligible for inclusion: a change in haemoglobin (Hb); the
How were decisions on the relevance of primary studies made?
Two reviewers independently selected studies for inclusion and resolved any disagreements by consensus.

Assessment of study quality
Higher quality trials were defined as those that were randomised, double-blind, and met pre-defined limits for exclusions and withdrawals (full details were given in the report). Details pertaining to allocation concealment and reporting of reasons for exclusions were also assessed. Two reviewers evaluated study quality as part of the data extraction procedure.

Data extraction
Two reviewers independently extracted data onto database forms that were then compared electronically. Any disagreements were resolved by consensus. The data extracted included the number of patients enrolled and the number evaluable, type of malignancy, chemotherapy and radiotherapy regimens, age, history of transfusion and iron supplementation, and reported predictors of response to epoietin. The outcomes data included the duration over which transfusion outcomes were measured. Partial and complete response were taken as defined in the original studies. Data on epoietin-related adverse events were extracted only if the proportions of patients who experienced the event in the treatment and control groups were both reported. If exact values were not reported, they were estimated from figures where possible. Reported P-values for differences between the treatment and control groups were extracted; if not reported, the reviewers calculated them where possible using a chi-squared test or Fisher's exact test.

Methods of synthesis
How were the studies combined?
The studies were combined through meta-analysis, using a random-effects model, to estimate a pooled odds ratio (OR) and 95% confidence intervals (CIs) for transfusion in patients with anaemia primarily due to cancer therapy. Other results were combined in a narrative synthesis. The analyses were based on the number of patients who were evaluable, not the number enrolled.

How were differences between studies investigated?
The studies were grouped according to the mean or median baseline Hb (Hb threshold): at least 12 g/dL; more than 10 g/dL, but less than 12 g/dL; 10 g/dL or less. Differences due to patient characteristics were explored in the narrative synthesis: haematological malignancy versus solid tumours; chemotherapy with or without platinum, chemotherapy and/or radiotherapy; adult, paediatric, geriatric; prior versus no prior transfusion; iron supplementation versus no supplementation.

In the meta-analysis a chi-squared test was used to assess statistical heterogeneity and a sensitivity analysis was conducted to investigate the effect of study quality. The epoietin dose regimen, dose range and treatment duration were also examined (independently of study quality).

Results of the review
For anaemia primarily due to chemotherapy and/or radiotherapy, 22 trials (1,927 enrolled, 1,838 evaluable) were included. Eighteen were RCTs (1,616 evaluable), two used concurrent controls (96 evaluable), and two used historical controls (126 evaluable).

For anaemia primarily due to cancer itself, 6 RCTs (693 enrolled, 648 evaluable) were included.

For allogenic stem cell transplantation, 7 trials (493 enrolled, 474 evaluable) were included. Five were RCTs (387
evaluable) and two used historical controls (87 evaluable).

For autologous stem cell transplantation, 6 trials (321 enrolled, 319 evaluable) were included. Three were RCTs (169 evaluable) and three used historical controls (150 evaluable).

Only the main results are summarised here; further analyses of epoietin administration, effects of patient characteristics, and reported predictors of response were available in the full report.

Anaemia primarily due to chemotherapy and/or radiotherapy.

Epoietin increased levels of Hb and the rate of haematologic response. A meta-analysis of 12 RCTs (n=1,390) in which epoietin was given subcutaneously showed a statistically significant reduction in the odds of transfusion with epoietin (OR 0.38, 95% CI: 0.28, 0.51). There was statistically significant heterogeneity between the trials (P=0.099). When only the 5 highest quality RCTs (n=771) were pooled, the difference in effect was less but still statistically significant (OR 0.45, 95% CI: 0.33, 0.62). The number-needed-to-treat (NNT) based on the higher quality trials suggested that 6 patients (between 4 and 9) would need to be treated with epoietin for one patient to avoid transfusion (NNT 5.2, 95% CI: 3.8, 8.4). The inclusion of an additional 2 trials in the meta-analysis, in which epoietin was given intravenously, did not change the findings. The available data were insufficient to determine the effect of baseline Hb or initiating epoietin treatment at Hb thresholds higher than 10 g/dL. One RCT showed an improvement in quality of life with epoietin, but there were insufficient data to assess the quality of the study or the clinical significance of its findings. Evidence of the effect of epoietin dose regimen, dose range or treatment duration was inconclusive. Among the adverse events reported, only fatigue was statistically significantly different (based on 4 trials); this was more common among the control group. There were more withdrawals due to adverse events among epoietin-treated patients (8 trials), but the difference was not statistically significant (P=0.07).

Anaemia primarily due to cancer itself.

Three studies that reported transfusion outcomes suggested a favourable effect of epoietin, but the reduction in the need for transfusion was statistically significant in only one study. Significantly more epoietin-treated patients than controls achieved a haematological response in all studies. The limited evidence from one study suggested that the response may be lower in patients with myelodysplastic syndrome. Epoietin increased Hb levels in all studies, but the difference was not always statistically significant. It was not possible to determine the effect of initiating epoietin treatment at different Hb thresholds because all patients had a baseline Hb of 10 g/dL or less. There were insufficient data to assess the effect of epoietin on quality of life. In terms of adverse events, only hypertension was significantly more common with epoietin (based on 3 trials; P=0.01).

Allogenic stem cell transplantation. Epoietin decreased the time to RBC engraftment by one or two weeks and may have decreased the number of RBC units transfused. There was no significant difference in the duration of hospitalisation (2 trials). The reporting of adverse events was sparse.

Autologous stem cell transplantation. Epoietin was not shown to have a beneficial effect on RBC engraftment or transfusion, or the length of hospitalisation. The reporting of adverse events was sparse.

Cost information
Cost data from trials that met the inclusion criteria were to be included, however, none reported cost data.

Authors’ conclusions
The authors’ conclusions reiterated their results. Briefly, epoietin had a beneficial effect on haematological response in patients with anaemia due to cancer or cancer therapy, and reduced transfusion among patients with anaemia due to cancer therapy. The evidence suggested a beneficial effect of epoietin on RBC engraftment among patients with anaemia resulting from bone marrow ablation prior to allogenic stem cell transplantation, but not prior to autologous stem cell transplantation. The evidence on quality of life and adverse events was limited in all settings.
CRD commentary
The methodology of this review was rigorous. The review questions were defined clearly. The search for studies was extensive, although there is some possibility of publication bias (which can overestimate treatment effect) since the data had to be published in abstract form at least to be included. Steps were taken to minimise bias when selecting the studies for inclusion and to protect against errors in the data extraction process. Appropriate methods were used to combine the studies, and study quality and differences between the studies were taken into account. The results (which comprise the authors' conclusions) appear balanced and to have been based on the evidence presented.

Implications of the review for practice and research
Practice: There was no explicit statement about practice in the report. However, the authors stated that the American Society for Hematology and the American Society for Clinical Oncology intended to use the findings of this review to develop clinical guidelines for their members.

Research: The authors stated that adequately powered RCTs are needed to determine whether additional benefits in transfusion reduction and quality of life can be gained by initiating epoetin treatment at baseline Hb levels of higher than 10 g/dL. In addition, a higher standard of methodological quality and reporting is required to enable a reliable estimation of the treatment effect, particularly on quality of life. More evidence on which characteristics predict haematologic response to epoetin, particularly among patients with myelodysplastic syndrome, is needed. The optimal initial dose of epoetin has yet to be established.

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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.