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

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CRD summary
This review evaluates the clinical effectiveness and safety of erythropoiesis-stimulating proteins for the treatment of chemotherapy-induced anaemia. The reviewers concluded that there are no clinically relevant differences between epoetin and darbepoetin. However, concerns about the robustness of the pooled effect sizes suggest that the findings should be interpreted with caution.

Authors' objectives
To evaluate the clinical effectiveness and safety of erythropoiesis-stimulating proteins (ESPs) for the treatment of chemotherapy-induced anaemia (CIA).

Searching
A previous literature search (1980 to 1999) was updated. MEDLINE was searched from 1999 to 2005 using the reported search terms. Additional searches for the 6-month period up to 10th July 2005 were carried out using Current Contents, PubMed and the Cochrane Library. The reference lists of included papers and recent reviews or meta-analyses were also searched manually. No attempts were made to contact authors or manufacturers for unpublished material. Only full papers published in the English language between 1980 and July 2005, or abstracts from the 2003, 2004 and 2005 annual meetings of the American Society of Clinical Oncology, the American Society of Hematology, or the European Society of Medical Oncology were eligible for inclusion.

Study selection
Study designs of evaluations included in the review
Randomised and non-randomised controlled trials with at least 10 participants per treatment group were eligible for inclusion. Prospective uncontrolled studies with at least 300 participants were also eligible for inclusion in the assessment of efficacy and safety.

Specific interventions included in the review
Studies of ESPs including epoetin (EPO; alpha and beta) and darbepoetin-alpha (DARB) were eligible for inclusion. The interventions had to be compared with standard care (i.e. transfusions) and/or placebo, or compared with an alternative ESP (for controlled trials) or no comparator (for community studies). The dose regimens of ESPs varied: for EPO, from daily to once weekly administration of 100 to 600 U/kg for weight-based studies and 1,000 to 60,000 U for fixed-dose studies; for DARB, administration every week to every 3 weeks with weight-based doses of between 1 and 15 microg/kg (details were reported).

Participants included in the review
Studies of adults and children with CIA were eligible for inclusion. Patients with CIA were defined as having a haemoglobin (Hb) level of below 11 g/dL. Amongst the studies included in the review of effectiveness, the mean baseline Hb ranged from 8.3 to 11.0 g/dL; studies eligible for inclusion in the assessment of safety were allowed baseline levels exceeding 11 g/dL. Treatment was usually stopped (where reported) when Hb levels were between 12 and 15 g/dL; only 25% of the studies required Hb levels to exceed 13 g/dL before stopping treatment. Where reported, the mean age of the patients ranged from 3.2 to 88 years and the tumour types included both solid and haematological tumours. Patients received various chemotherapy treatment regimens including non-platinum regimens, platinum regimens, anthracycline-based regimens and various other unspecified regimens, ranged in duration from 9 to 28 weeks.

Outcomes assessed in the review
Studies reporting clinically relevant outcomes for effectiveness and safety were eligible for inclusion. Such outcomes
included the number of patients requiring red blood cell transfusions, changes in quality of life, study mortality (treatment-related and/or all-cause), and the number of patients with venous thromboembolism (VTE). Eligible VTE events included deep vein thrombosis, pulmonary embolism, or any other thromboembolic event measured either passively or actively; confirmation could be by clinical, radiographic or pathologic methods. Eligible measures of quality of life included the Functional Assessment of Cancer Therapy - Fatigue (FACT) subscale, any other linear analogue self assessment (LASA) scale measuring overall fatigue, a visual analogue scale, or the Cancer Linear Analogue Scale.

How were decisions on the relevance of primary studies made?
Two reviewers independently selected and agreed upon articles for inclusion in the review.

Assessment of study quality
The validity of randomised controlled trials (RCTs) that were published in full was assessed using the Jadad scale. A maximum of 5 points was awarded for the method of randomisation, the use of blinding and the assessment of withdrawals. Two reviewers assessed and agreed upon the final quality scores for each study.

Data extraction
Two reviewers extracted and agreed upon the data using extraction forms specially developed for the project. Intention-to-treat values were recorded for study and patient demographics. Quality of life scales were standardised to a 0 to 100 common scale. For safety data, zero events were only recorded where reported and, for the purposes of statistical calculations, '0.25' was substituted for '0' in the respective 2x2 tables. Odds ratios (ORs) were calculated for categorical outcomes and standardised mean differences for continuous outcomes; 95% confidence intervals (CIs) were reported.

Methods of synthesis
How were the studies combined?
Studies that compared EPO or DARB with the same-study control group were grouped according to outcome and intervention, then pooled to calculate weighted mean differences (WMDs) or ORs using both fixed-effect and random-effects meta-analyses. Data from the prospective uncontrolled studies were considered separately, and the weighted means of frequencies and absolute differences from baseline to end point were calculated.

How were differences between studies investigated?
Differences between the studies were assessed using the Cochran Q test. Sensitivity analyses were also performed using jackknife analyses, meta-regression analyses and subgroup analyses where appropriate. Covariates included geographical location, industry sponsorship, level of evidence, year of study, size of study, population type (i.e. child or adult), gender, age, baseline Hb, and type of tumour (solid or haematological).

Results of the review
Forty studies (n=21,378) were included: 30 RCTs (n=6,149), 2 non-randomised controlled studies (n=3,158) and 8 uncontrolled studies (n=12,071).

Fifteen studies (out of the 25 RCTs assessed) scored less than 4 points out of 5 for validity. Twenty-nine of the 40 studies received some form of industrial sponsorship.

A significant reduction in the requirement for red blood cell transfusions was found for patients treated with EPO in comparison with those receiving placebo or standard care (16 studies; OR 0.44, 95% CI: 0.35, 0.55). No significant differences were found when EPO was compared with DARB (5 studies). None of the covariates investigated had a significant effect on the need for blood transfusion.

Patients treated with EPO (versus standard care or placebo) showed statistically significant improvements in quality of life when using the FACT subscale (4 studies; WMD 0.23, 95% CI: 0.10, 0.36) and the LASA scale (4 studies; WMD 0.36, 95% CI: 0.14, 0.57). No significant differences in quality of life were found when EPO was compared with
DARB (2 studies).

No statistically significant differences in either the risk of VTE or death were found between DARB and control (based on 1 study for VTE and 3 studies for mortality), between EPO and control (based on 5 studies for VTE and 8 studies for mortality), or between EPO and DARB (based on 1 study for each outcome).

Authors' conclusions
No clinically relevant differences were found between epoetin and darbepoetin.

CRD commentary
This review was based on a clear research question with adequately defined inclusion criteria. The literature search updated a previous search, but excluded unpublished material and any information not published in English. This suggests that the review may be subject to publication and language bias. However, attempts were made to reduce the risks of bias and error during the selection and assessment stages of the review, with two reviewers validating each stage of the review process. Validity was assessed using an established checklist, although only the composite score was presented; this makes it difficult for readers to judge the study validity for themselves.

Reasonable attempts were made to examine potential sources of heterogeneity within the analyses. However, it is still possible that other potential sources of heterogeneity might not have been investigated, and the authors states that poor reporting of study details was often a problem when comparing the studies. Extensive statistical pooling was carried out for each outcome, but although meta-analysis graphs were presented for the main analyses, estimates of statistical heterogeneity were not reported. Given the variations in drug treatments, dosage schedules, participant characteristics and study designs, it is unclear whether these combined effect sizes were appropriate. Although the data presented seems to suggest that, overall, EPO is better than control, the evidence for DARB is more limited and evidence about the comparative efficacy of EPO and DARB tended to be based on a small number of controlled studies. Given the aforementioned concerns, the pooled effect sizes for both drugs should be interpreted with caution.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that further studies are required to optimise the use of ESPs and to investigate potential predictors of response, optimal dose regimens and the use of iron supplementation. Such studies should adequately report their methods and use dose regimens in accordance with current labelling and/or clinical practice. Research is also needed to define the role of ESPs in anaemic cancer patients who are not receiving chemotherapy.

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