The role of erythropoietin in the management of cancer patients with non-hematologic malignancies receiving chemotherapy

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CRD summary
The data presented in this review support the authors' conclusions that erythropoietin safely reduces the incidence of symptomatic treatment-related anaemia and the need for blood transfusion. The use of erythropoietin is recommended where a slow decline in haemoglobin is associated with increased fatigue and reduced quality of life, but not where rapid recovery of haemoglobin is required.

Authors' objectives
To investigate whether erythropoietin reduces the need for transfusion of red blood cells and improves quality of life in people with non-haematologic malignancies who are receiving chemotherapy for cancer.

Searching
MEDLINE (from 1966 to January 2003), Cancerlit (from 1983 to October 2002), the Cochrane Library (Issue 4, 2002), PDQ, conference proceedings of meetings of the American Society of Clinical Oncology (1997 to 2002), CMA Infobase: Clinical Practice Guidelines, the National Guideline Clearinghouse, and reference lists from articles and reviews were searched; the search terms were reported. Studies published in a language other than English were excluded.

Study selection
Study designs of evaluations included in the review
Randomised trials were eligible for inclusion. Non-randomised trials containing information about quality of life were also eligible. Both full reports and published abstracts were considered. The authors also included meta-analyses and practice guidelines.

Specific interventions included in the review
Studies that compared erythropoietin with placebo or observation were eligible for inclusion in the review. The varied doses and regimens were detailed in the review. The most common dose of erythropoietin was 150 IU/kg subcutaneous, three times per week. Platinum- and non-platinum-based chemotherapy regimens were used. Studies were excluded if they focused on people receiving radiotherapy or chemoradiotherapy.

Participants included in the review
Studies were eligible for inclusion if they included people with non-haematologic malignancies undergoing chemotherapy. The target participants had haemoglobin levels no greater than 100 g/L during the initial courses of myelosuppressive cancer chemotherapy or haemoglobin levels no greater than 120 g/L with symptoms of anaemia affecting functional capacity or quality of life; and anaemia related directly or indirectly to malignancy, but not caused by haemolysis, gastrointestinal bleeding, or iron or folate deficiencies. The included studies comprised both children and adults. The tumour types included gynaecological, bone, solid, and multiple types. Studies were excluded if they focused on people with haematologic malignancies originating in bone marrow.

Outcomes assessed in the review
Studies were eligible for inclusion if they contained information about the number of people receiving transfusions during follow-up, change in haemoglobin level, adverse effects, or quality of life. Quality of life was measured using structured scales, most commonly the cancer-specific Linear Analog Scale Assessment, Functional Assessment of Cancer Therapy - General, the Functional Assessment of Cancer Therapy - Anaemia, the Medical Outcomes Short Form-36, the Nottingham Health Profile, and the QLQ-C30.

How were decisions on the relevance of primary studies made?
A medical oncologist, a member of the Systemic Treatment Disease Site Group, and methodologists selected and
reviewed the studies.

Assessment of study quality
The authors did not state that they assessed validity. This review was developed using the Practice Guidelines Development Cycle, which has been reported elsewhere (see Other Publications of Related Interest).

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. Data were extracted on the participant numbers and characteristics, treatment regimen, study entry criteria, outcomes, and publication details.

Methods of synthesis
How were the studies combined?
The authors performed a meta-analysis with data from 19 of the 23 identified trials. These 19 trials included information on the number of people receiving transfusions during follow-up. Risk ratios, 95% confidence intervals (CIs), and relative risk reductions were calculated. The authors used a random-effects model due to suspected statistical heterogeneity across the studies. Other findings were reported narratively.

How were differences between studies investigated?
The authors reported statistical tests (chi-squared) for heterogeneity when assessing the proportion of participants transfused. They also performed sensitivity analyses to determine whether the following characteristics might impact on the treatment effect: use of placebo-controlled studies including people with documented anaemia when the trial began; studies including people with normal haemoglobin levels at the start of the trial; and the use of platinum- and non-platinum-based chemotherapy. Data on quality of life were reported separately for randomised and non-randomised trials.

Results of the review
The authors included one meta-analysis, 23 randomised trials with 2,462 participants comparing erythropoietin with placebo (9 trials) or observation (14 trials), one randomised trial comparing two doses of erythropoietin, and 10 non-controlled trials with data on quality of life. The sample size in the randomised trials ranged from 17 to 375.

In pooled data from 19 randomised trials (21 comparisons with 1,745 participants), erythropoietin reduced the relative risk of transfusion by 44% (relative risk 0.56 in favour of erythropoietin, 95% CI: 0.47, 0.66, P<0.00001). The benefits remained across five sensitivity or subgroup analyses. Evidence supporting erythropoietin appeared to be stronger for people receiving platinum-based therapy, but erythropoietin was also effective in people receiving moderately or severely myelosuppressive regimens that did not contain platinum.

Adverse effects related to erythropoietin were rare and mild. No significant differences in adverse effects were detected between groups in randomised trials. The long-term adverse effects remain uncertain.

Eight randomised controlled trials and 10 non-controlled trials measured quality of life. People receiving erythropoietin had improved quality of life according to a number of measures.

Further detailed analyses were reported in the review.

Authors’ conclusions
Erythropoietin safely reduces the incidence of symptomatic treatment-related anaemia and the need for red blood cell transfusion. The use of erythropoietin is recommended for people in whom a slow decline in haemoglobin is associated with increased fatigue and reduced quality of life. Erythropoietin is not recommended where rapid recovery of haemoglobin (i.e. less than 4 weeks) is required.
CRD commentary
This review had well-defined research questions, inclusion and exclusion criteria, and a comprehensive search strategy. The review was limited to English language studies, which may have introduced some language bias. Decisions about which articles to include were made by consensus from at least two people. However, the authors did not indicate how they assessed the validity of the included studies, if at all. It is difficult to assess the overall quality of the included studies and of the review itself, given the lack of information about a validity assessment.

The authors clearly addressed their research questions, reported sufficient details of the primary studies, and narratively synthesised the data in a constructive and concise format. The pooled analysis of transfusion rates appears appropriate. However, the authors did not report the average follow-up period over which the transfusion rates were monitored. The authors mentioned suspected heterogeneity between the studies, but did not identify potential sources of heterogeneity. They conducted sensitivity analyses to ensure that their findings were consistent among different subgroups.

Overall, the data presented support the authors’ conclusions.

Implications of the review for practice and research
Practice: The authors stated that erythropoietin is a safe and effective treatment option if given with the intent of reducing the incidence of symptomatic treatment-related anaemia and the need for red blood cell transfusion. Erythropoietin is a reasonable option for people in whom a slow decline in haemoglobin is associated with increased fatigue and perceived reductions in quality of life. It is not recommended in situations where recovery of haemoglobin is required in less than 4 weeks. Evidence supporting erythropoietin is stronger for people receiving platinum-based therapy, but erythropoietin is also effective in people receiving moderately or severely myelosuppressive regimens that do not contain platinum. Erythropoietin may be most useful for people who have a reasonable chance of long-term survival or cure from chemotherapy, because these people have the greatest risk of suffering long-term complications from transfusion.

Research: The authors suggested that randomised trials are needed to assess whether erythropoietin raises haemoglobin and improves quality of life in people with cancer who are not receiving chemotherapy, or are receiving only radiotherapy.

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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.