Recombinant human erythropoietin in pediatric oncology: a review

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Authors' objectives
To summarise and analyse the clinical information currently available on the use of epoetin in children with cancer.

Searching
Cancerlit and MEDLINE were searched using the keywords listed in the review. In addition, the reference lists of extensive articles published in major journals were searched manually. The search was restricted to publications in the English language.

Study selection
Study designs of evaluations included in the review
Clinical trials were included in the review. The authors did not state explicit exclusion criteria relating to the study design. However, one study was excluded as it reported only one patient, while another was excluded because there were only four patients and the results were not evaluable. Two studies were excluded because they had overlapping patients, making it unclear whether the patients were reported twice. The studies included were randomised controlled trials (RCTs) and open phase I/II single-institution trials.

Specific interventions included in the review
The review included clinical trials of epoetin treatment. The dosages ranged from 25 to 400 IU/kg, although most trials initiated epoetin at 150 IU/kg. The schedule of administration was daily (1 trial) or three times a week (7 trials). The duration of treatment ranged from 14 days to 11 months. The route of administration was subcutaneous (4 trials), subcutaneous or intravenous (3 trials), or not stated (1 trial). Iron supplements were given in 5 trials, but were not permitted in one trial.

Participants included in the review
The review included clinical trials involving paediatric cancer patients. The authors did not state explicit exclusion criteria relating to the participants. However, 3 studies were excluded as they focused only on patients who received bone marrow transplants. Specific diagnoses of participants in the included studies were acute leukaemia, acute lymphocytic leukaemia (ALL), non-Hodgkin lymphoma, central nervous system (CNS) tumours and several types of non-CNS solid tumours. One study did not specify the type of solid tumour, while another did not specify the type of cancer.

Outcomes assessed in the review
The authors did not specify any inclusion criteria relating to the outcome. The outcome measured was response to epoetin, which included haemoglobin levels, reticulocyte counts and transfusion requirements.

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

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 number of patients receiving epoetin (or the number of courses), diagnosis, intervention, control and results.
Methods of synthesis
How were the studies combined?
A narrative synthesis of the studies was undertaken.

How were differences between studies investigated?
Heterogeneity was not formally assessed. However, the authors stated that much variation was evident in the analysed reports.

Results of the review
Eight studies were included in the review: 4 RCTs and 4 open phase I/II single-institution trials. The number of participants in the trials was not reported, only the number of participants who received epoetin or, in one trial, the number of courses. In the RCTs, the total number of participants who received epoetin (or courses) was 68; 96 patients received epoetin in the open trials.

Five of the 8 studies reported a benefit with epoetin treatment, including 3 RCTs where the differences between the treatment groups were significant. One RCT did not report significant differences in overall response to epoetin-alpha in patients with ALL, although treatment with epoetin-alpha was significantly more effective in patients with low-risk ALL. One open study reported increased haemoglobin levels and reticulocyte counts during epoetin-alpha administration, although no statistics were reported. The other open study concluded that epoetin-alpha was not effective, on the basis of increased haemoglobin and transfusion requirements.

Authors’ conclusions
Epoetin-alpha appeared to be an effective and safe treatment for anaemia in paediatric cancer patients. Randomised controlled clinical trials and open trials have shown that the use of epoetin-alpha results in increased haemoglobin levels and decreased transfusion requirements. However, these observations were based on limited clinical data (less than 100 treated children). More clinical trials in children with cancer are needed; three are currently underway.

CRD commentary
This review was based on a well-defined question, but it did not state explicit inclusion or exclusion criteria relating to the study design, participants, intervention or outcomes of interest. The authors only searched two electronic databases and the reference lists of extensive articles published in major journals. The computerised searches were limited to English language literature and no attempts were made to identify unpublished studies. In addition, there was no assessment of publication bias. It is highly likely that relevant studies were missed by this search strategy.

The trials do not appear to have been assessed for quality. The authors did not report details of the study selection and data extraction processes, which could allow the introduction of errors and reviewer bias. Six of the included trials were discussed in detail. However, important data were still overlooked for some trials, such as the number of patients in the control groups.

Heterogeneity between the studies was not statistically assessed. However, the authors reported that they made no attempt at a meta-analysis because much variation was evident in the reports. A narrative synthesis was therefore appropriate. The conclusions of this review should be interpreted with caution due to the limitations highlighted.

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

Research: The authors stated that numerous issues need to be addressed in future trials of children with cancer and anaemia. One of the most important is the determination of the best epoetin-alpha dose relative to dose and schedule; another is the administration of iron supplements. To date there are no data concerning quality of life in children, but this is an important outcome to address. Three multicentre randomised studies of the use of epoetin-alpha in children with cancer- and chemotherapy-associated anaemia are underway; some of the aforementioned issues are being
addressed in these studies.

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