A systematic review and economic evaluation of epoetin alfa, epoetin beta and darbepoetin alfa in anaemia associated with cancer, especially that attributable to cancer treatment

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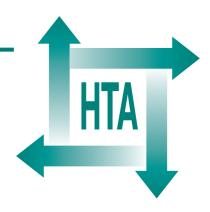
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Executive summary

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Background

Cancer-associated and cancer-treatment-associated anaemia are important problems which have been under appreciated in the past. Management has consisted of investigation of the cause of anaemia, monitoring, blood transfusions and treatment of the underlying cancer. Epoetin alfa, epoetin beta and darbepoetin alfa are three types of exogenous erythropoietin which stimulate the bone marrow to produce red blood cells. They are expensive, with each month of treatment costing around £1000, and patients often requiring 3-6 months of treatment. The cost of alternative treatment, such as red blood cell transfusion (RBCT), is also often underestimated, with the approximate cost per typical transfusion (2 or 3 units), including administration, but not cost to patient and donor, recently being estimated as £635. Increasing scarcity of blood is a further concern.

Objective

To assess the effectiveness and cost-effectiveness of epoetin alfa, epoetin beta and darbepoetin alfa (referred to collectively in this report as epo) in anaemia associated with cancer, especially that attributable to cancer treatment.

Methods

Using a recently published Cochrane review as the starting point, a systematic review of recent randomised controlled trials (RCTs) comparing epo with best standard was conducted. MEDLINE, EMBASE, the Cochrane Library and other databases were searched from 2000 (1996 in the case of darbepoetin alfa) to September 2004. Inclusion, quality assessment and data abstraction were undertaken in duplicate. Where possible, meta-analysis was employed.

The economic assessment consisted of a systematic review of past economic evaluations, an assessment of economic models submitted by the manufacturers of the three epo agents and development of a new individual sampling model (the Birmingham epo model).

Results

Effectiveness

A total of 46 RCTs was included in this systematic review, 27 of which had been included in the Cochrane systematic review. All 46 trials compared epo plus supportive care for anaemia (including transfusions) with supportive care for anaemia (including transfusions) alone. Outcomes assessed were anaemia-related outcomes [haematological response, haemoglobin (Hb) change, RBCT requirements], adverse events, health-related quality of life (HRQoL) and malignancy-related outcomes (tumour response, overall survival).

Haematological response (defined as an improvement by 2 g dl⁻¹) had a relative risk of 3.4 [95% confidence interval (CI) 3.0 to 3.8, 22 RCTs] with a response rate for epo of 53%. The trial duration was most commonly 16–20 weeks. There was little statistical heterogeneity in the estimate of haematological response, and there were no important differences between the subgroups examined. Hb change showed a weighted mean difference of 1.63 g dl⁻¹ (95% CI 1.46 to 1.80) in favour of epo. Treatment with erythropoietin in patients with cancer-induced anaemia reduces the number of patients who receive an RBCT by an estimated 18%.

HRQoL data were analysed using vote counting and qualitative assessment, and a positive effect was observed in favour of an improved HRQoL for patients on epo. Published information on side-effects was of poor quality. New trials provided further evidence of side-effects with epo, particularly thrombic events, but it is still unclear whether these could be accounted for by chance alone.

The results of the previous Cochrane review suggested a survival advantage for epo, with a hazard ratio (HR) of 0.84 (95% CI 0.69 to 1.02), based on 19 RCTs. The update, based on 28 RCTs, suggests no difference (HR 1.03, 95% CI 0.88 to 1.21) (variance estimate inflated for substantive heterogeneity, $\chi^2 = 37.75$, 27 df, p = 0.08; HR using standard method 1.03, 95% CI 0.92 to 1.16, p = 0.57; $\chi^2_{(het)} = 37.74$, 27 df, p = 0.08). Subgroup analysis suggested some explanations for this heterogeneity, but it is difficult to draw firm conclusions without access to the substantial amounts of missing or unpublished data, or more detailed results from some of the trials with heterogeneous patient populations. The conclusions are, however, broadly in line with those of a Food and Drug Administration (FDA) safety briefing, which recommended that patients with Hb above 12 g dl⁻¹ should not be treated; the target rate of rise in Hb should not be too great, and further carefully conducted trials are required to determine which subgroups of patients may be harmed by the use of these products, in particular through the stimulation of tumour activity.

Cost-effectiveness

Five published economic evaluations identified from the literature had inconsistent results, with estimates ranging from a cost per quality-adjusted life-year (OALY) under £10,000 through to epo being less effective and more costly than standard care. The more favourable evaluations assumed a survival advantage for epo. The three company models submitted each relied on assumed survival gains to achieve relatively low cost per QALY, from £13,000 to £28,000, but generated estimates from £84,000 to £159,000 per QALY when no survival gain was assumed. Each of these models relied on Hb levels alone driving utility, and each assumed gradual normalisation of Hb in the standard treatment arm after the end of treatment. The Birmingham epo model followed the company models in regard to the relationship between Hb levels and utility, and also assumed normalisation in the base case. With no survival gain, the incremental cost per QALY was £150,000 falling to £40,000 when the lower, more favourable, confidence interval for survival was used.

Conclusions

Epo is effective in improving haematological response and RBCT requirements, and appears to have a positive effect on HRQoL. The incidence of side-effects and effects on survival remains highly uncertain. If there is no impact on survival, it seems highly unlikely that epo would be considered a cost-effective use of healthcare resources.

Recommendations for research

The following areas are suggested for further research.

- The main target of further research should be to improve estimates of impact on survival. In the first instance this should be through more detailed secondary research, such as the individual patient data meta-analysis started by the Cochrane group.
- Further trials may be required, and have been recommended by the FDA. However, many trials are in progress, completed but unreported or awaiting mature follow-up.
- The Birmingham epo model developed as part of this project has features that are not present in previous models. These features improve its flexibility in exploring different scenarios in the future. Funding is needed to support further refinement and validation of this work.
- Finally, further research to resolve uncertainty about other parameters, particularly quality of life and adverse events, should be pursued in parallel with attempts to improve evidence on survival. The rate of normalisation was also an important parameter in the model for which no published data source was identified, and so further research in this area would be beneficial.

Publication

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NIHR Health Technology Assessment Programme

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