

**Clinical and Cost
Effectiveness of Darbepoetin
alfa in
Cancer Treatment-induced
Anaemia**

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EXECUTIVE SUMMARY

Aim

To assess the clinical and cost-effectiveness of darbepoetin alfa in anaemia associated with cancer, particularly anaemia attributable to cancer treatment

Background

Anaemia is a frequent complication of cancer and its treatment, in particular, anaemia associated with myelosuppressive chemotherapy, which may affect as many as 50% of patients receiving chemotherapy. The incidence and severity of anaemia varies according to tumour type and chemotherapy regimen, increasing over the course of chemotherapy. Anaemia is a debilitating condition associated with increased morbidity and reduced health-related quality of life (HRQoL). Anaemia is associated with poor response to cancer treatment and reduced survival. Treatments for chemotherapy-induced anaemia (CIA) aim to increase haemoglobin (Hb) towards normal range, maintain these levels during treatment, reduce morbidity, and improve HRQoL.

Current Service Provision

Treatment for CIA in the UK includes blood transfusions, iron management, and erythropoietic agents (EAs). Blood transfusions, the most commonly used treatment for CIA in the UK, are an effective, reliable treatment for the rapid correction of anaemia, but they have limitations and risks: fluctuating Hb, short-lived effect, requirement for hospitalisation, risk of infection and/or allergic reactions, and potential limited availability. Hence, blood transfusions generally are reserved for acute life-threatening situations; patients with severe anaemia (Hb <8.0 g/dL) or at risk of cardiovascular complications. If changes in the availability of blood products occur in the UK (and treatment of mild-to-moderate anaemia becomes a consideration), treatment strategies to reduce the need for transfusion will increase in importance.

EAs are an effective treatment for CIA, but their use in the UK, relative to use in other European countries, is low. Three recombinant EAs are licensed in England and Wales for the management of CIA: darbepoetin alfa, epoetin alfa, and epoetin beta. At licensed starting doses, these EAs are equivalent in acquisition cost. Darbepoetin alfa (Aranesp®) is biochemically distinct from epoetin (alfa and beta) and has a greater *in vivo* biologic activity and longer half-life, allowing less-frequent administration. Darbepoetin alfa is the only EA licensed for dosing once every 3 weeks (Q3W) or alternatively, on a once-weekly basis (QW), in anaemic patients with solid tumours and lymphoproliferative disorders, irrespective of chemotherapy type or endogenous erythropoietin level.

Currently, limited groups of patients with CIA receive EA therapy because of local funding availability or religious objections to the use of blood products. Thus, there is not equity of access to treatment with EAs for all patients with CIA in England and Wales.

Clinical Effectiveness of Erythropoietic Agents

Haematological Response: Darbepoetin alfa-treated patients had a significantly increased haematological response (relative risk [RR] 3.30; 95% CI 2.53-4.32; $p < 0.0001$; pooled results of 4 trials; $n=759$). In a combined analysis for all 18 trials of EAs, use of EAs significantly increased haematological response in patients with malignant disease, (RR 3.53; 95% CI 3.08-4.05; $p < 0.0001$; independent of transfusion). Treatment with darbepoetin alfa also resulted in a significantly increased haematopoietic response (RR 2.64; 95% CI 2.17-3.21; $p < 0.0001$; pooled results of 4 trials $n=759$).

Red Blood Cell Transfusions: Darbepoetin alfa-treated patients had a significantly reduced risk of receiving a red blood cell (RBC) transfusion (RR 0.69; 95% CI 0.59-0.81; $p < 0.0001$; pooled results of 4 trials; $n=759$). Patients treated with darbepoetin alfa generally received 1.1 units of blood less than the control group (weighted mean difference [WMD] -1.10; 95% CI -1.70 to -0.51; $p=0.0003$; pooled results of 4 trials; $n=759$). This result is consistent with pooled results from all EA trials showing that use of EAs significantly reduced the risk of receiving RBC transfusion (RR 0.67; 95% CI 0.63-0.72; $p < 0.0001$) and that patients treated with EAs generally received 1.0 unit of blood less than the control group (WMD -1.02; 95% CI -1.29 to -0.75; $p < 0.0001$; combined analysis of 17 trials; $n=2815$).

Health-related Quality of Life: HRQoL was assessed in 4 darbepoetin alfa trials using the FACT-F subscale. Pooled data from the 4 trials showed that patients treated with darbepoetin alfa were more likely to experience a clinically significant (3 point) change in FACT-F score than placebo treated patients (OR 1.36; 95% CI 0.98-1.90; $p=0.069$).

Tumour Response and Survival

Limited clinical data from EA randomised controlled trials (RCT) address tumour response and survival in anaemic cancer patients receiving chemotherapy. Most EA studies were not designed or powered to evaluate tumour response or survival. The effect of epoetins (alfa and beta) on tumour response and survival has been evaluated in a Cochrane review, and results of a further combined analysis of all EAs (including darbepoetin alfa) are reported. Two studies designed to prevent anaemia and maintain higher Hb values than currently licensed have reported negative survival outcomes for patients treated with EAs. These have led to strengthened warnings in the licences of all EAs to not treat above the approved Hb target of 12 g/dL and not higher limits.

Tumour Response: Pooled results of the combined analysis suggest that EAs improve complete tumour response (RR 1.35; 95% CI 1.09-1.66; $p=0.0057$; combined analysis of 11 trials; $n=1909$).

Survival: Analysis of pooled survival outcomes from EA studies suggest improved survival in patients treated with EAs, (hazard ratio [HR] 0.88; 95% CI 0.76-1.01; $p=0.069$; combined analysis of 23 trials; $n=3838$).

Adverse Events

The safety profile of darbepoetin alfa is well established with >415,000 patient years of experience (as of 30 June 2004). Pooled safety data from 4 darbepoetin alfa studies (n=759) show no statistically significant increase in the incidence of the adverse events of hypertension, haemorrhage or thrombocytopenia, rash/irritation/pruritus, or convulsions. The pooled analysis suggests EA therapy is associated with an increased risk of thrombotic events, consistent with the information on expected adverse drug reactions on product labels for all EAs. To date (1 November 2004), no cases of antibody-mediated pure red cell aplasia (PRCA) caused by darbepoetin alfa treatment have been reported.

Economic Analysis

The cost effectiveness (CE) of darbepoetin alfa for the treatment of CIA in cancer patients was compared with conventional intervention using blood transfusions from a NHS perspective. The decision tree model was based on clinical data (1,262 patients enrolled in 7 darbepoetin alfa trials). The reference case CE results generate an incremental cost per quality-adjusted life-year (QALY) of £159,339. If a survival benefit is included, the incremental cost is £23,546/QALY.

Sensitivity analyses on the assumptions included in the CE analysis demonstrate that the reference case is strongly dependent on the duration of the post-trial QALY benefit. The survival-based analysis is strongly dependent on the true size of the survival benefit, based on the 95% CI for the clinical overall survival estimate, CE-ratio ranges from £12,775 to £320,105.

The CE analysis presented does not compare 2 treatments with similar benefits, since patients treated with red blood cell (RBC) transfusion do not maintain significant increases in Hb during the trial period. To compare treatment costs under conditions of equal clinical benefit, clinical trial data were used to estimate the quantity of blood needed to achieve the same clinical endpoints as darbepoetin alfa.

If RBC transfusions were used to achieve a clinical benefit equivalent to darbepoetin alfa, patients would need to receive an extra 9.75 units of blood over 12 weeks. In this case, treatment with darbepoetin alfa becomes cost equivalent. Given the inconvenience of receiving multiple transfusions, darbepoetin alfa offers a considerable advantage.

Treatment with darbepoetin alfa is cost effective, excluding survival benefit, if limitations in blood supply place an opportunity value of £1,523 per unit of blood. In the event of a blood supply shortage, an opportunity cost to use blood to treat CIA rather than surgical or trauma patients could exist.

Treatment of CIA with darbepoetin alfa is cost effective at a £30,000/QALY threshold if:

- A survival benefit for EAs is included; incremental cost per QALY is £23,546

- Blood is used to achieve equivalent clinical outcomes to darbepoetin alfa, treatment with darbepoetin alfa is cost equivalent
- Limitations in blood supply place an opportunity value of £1,523 per unit of blood

Wider Implications of Technology

Implementation of the use of darbepoetin alfa for the treatment of CIA would have a budget impact of £6,000,000 in the first year if all patients with Hb <10 g/dL were offered treatment. This cost would increase to £88,000,000 after 5 years if all the chemotherapy-treated cancer patients with Hb <11 g/dL were treated with darbepoetin alfa following a NICE recommendation.

Darbepoetin alfa treatment for CIA will reduce the requirement for blood transfusions (by up to 28,000 units), improve the overall quality of anaemia management in the UK, reduce patients' fatigue, and improve patients' HRQoL. Unlike blood transfusions, darbepoetin alfa treatment does not require the use of a hospital bed and offers dosing simplicity and flexibility (SC administration and Q3W or QW dosing) that benefit patients, nursing staff, and the NHS. Use of darbepoetin alfa to treat CIA would save approximately 19,000 bed-days/year.

Awareness of potential changes to the availability of blood products in the UK and the limitations and risk associated with use of blood transfusion means that cancer patients with anaemia do not routinely receive adequate treatment. As patients become more involved in treatment-related decisions, their preferences will need to be taken into greater account.

Conclusions

Darbepoetin alfa is an effective, well-tolerated treatment for the management of anaemia and fatigue in cancer patients with CIA. Darbepoetin alfa reduces the requirements for blood transfusions, increases and maintains Hb, reduces fatigue, and improves patients' quality of life.

Darbepoetin alfa treatment is currently estimated to introduce an incremental cost per QALY of £159,339. If a survival benefit is included, the incremental cost is £23,546/QALY.

All EAs have comparable efficacy, tolerability profiles, and acquisition cost. The prolonged half-life of darbepoetin alfa offers Q3W dosing; darbepoetin alfa can be administered on the same day as chemotherapy, a benefit to patients, caregivers, hospital staff, and the NHS. The CE of EA treatment is strongly dependent on the effect of treatment on survival, which currently is estimated with uncertainty from pooled clinical trials data.