The effectiveness and cost-effectiveness of erythropoiesis-stimulating agents (epoetin and darbepoetin) for treating cancer treatment-induced anaemia (including review of technology appraisal no. 142): a systematic review and economic model

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Scientific summary

ESAs for treating cancer treatment-induced anaemia

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Scientific summary

Background

Anaemia is defined as a deficiency in red blood cells (RBCs). It is the most frequent haematological manifestation in patients with cancer: > 50% of all cancer patients will be anaemic regardless of the treatment received and approximately 20% of all patients undergoing chemotherapy will require a red blood cell transfusion (RBCT). There are a number of potential causal factors, which can be patient, disease or treatment related.

Anaemia is associated with many symptoms. These include dizziness, shortness of breath on exertion, palpitations, headache and depression. All affect health-related quality of life (HRQoL). Severe fatigue is probably the most commonly reported symptom and can lead to an inability to perform everyday tasks. However, fatigue in people with cancer can also have other causes, such as the disease itself, chemotherapy, radiotherapy, anxiety or depression.

Many people are anaemic when cancer is diagnosed, before any cancer treatment starts. The degree of anaemia caused by treatments such as chemotherapy often fluctuates depending on the nature of the treatment and the number of courses administered, but is typically at its worst 2–4 weeks after chemotherapy is given. Once cancer treatments are stopped, a period of 'normalisation' is likely, during which the haemoglobin (Hb) may return to pretreatment levels.

Options available for the management of cancer treatment-induced anaemia (CIA) include adjustments to the cancer treatment regimen, iron supplementation and RBCT. The majority of people who become anaemic do not receive any treatment for their anaemia, but those who become moderately or severely anaemic are usually given RBCTs. Complications related to RBCT include procedural problems, iron overload, viral and bacterial infections and immune complications. However, a small proportion of people are unable to receive RBCT (Jehovah's Witnesses and people with multiple antibodies to RBCs, as they have required regular RBCTs in the past).

Treatment landscape, 10 years on

Erythropoietin is a glycoprotein hormone that is produced mainly in the kidney and is responsible for regulating RBC production. Erythropoietin for clinical use is produced by recombinant DNA technology. Erythropoiesis-stimulating agents (ESAs) are used as an addition to, rather than as a replacement for, existing approaches to the management of anaemia induced by cancer treatment. RBCTs, in particular, may still be needed in people treated with ESAs.

Based on the previous assessment [Wilson J, Yao GL, Raftery J, Bohlius J, Brunskill S, Sandercock J, *et al.* 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. *Health Technol Assess* 2007;**11**(13)], National Institute for Health and Care Excellence (NICE) guidance [technology appraisal (TA)142] (NICE. *Epoetin Alfa, Epoetin Beta and Darbepoetin Alfa for Cancer Treatment-Induced Anaemia*. NICE technology appraisal guidance TA142. London: NICE; 2008) recommended the use of ESAs in combination with intravenous iron for the treatment of CIA in women with ovarian cancer receiving platinum-based chemotherapy with symptomatic anaemia (Hb $\leq$ 8 g/dl). The recommendation made in TA142 did not prohibit the use of other management strategies for the treatment of CIA, for example blood transfusion (NICE, 2008). In addition, guidance set out in TA142 recommended ESAs in combination with intravenous

iron for people with profound CIA who cannot be given blood transfusions (NICE, 2008). The ESA with the lowest acquisition cost should be used (NICE, 2008).

Although evidence at the time documented a clear improvement in haematological response and a reduction in the need for RBCTs associated with the use of ESAs, there was considerable uncertainty surrounding safety (in particular the frequency of thromboembolic events) and the impact on survival, giving rise to ongoing debate about the effectiveness and safety of ESAs in this area. Ten years on from the previous appraisal (2004), licences have been amended to reflect these concerns.

Initially, all ESAs were recommended for use at Hb levels of ≤ 11 g/dl, with target Hb levels not exceeding 13 g/dl. A safety review by the Pharmacovigilance Working Party at the request of the Committee for Medicinal Products for Human Use in 2008 resulted in changes to the Summary of Product Characteristics for all ESAs at the European Medicines Agency's (EMA) request. These changes came into effect in 2008 – after the previous guidance was issued – and included a decrease in the Hb value for treatment initiation to ≤ 10 g/dl; amendment of the Hb target values to 10–12 g/dl; and amendment of Hb levels for stopping treatment to > 13 g/dl. In addition, the EMA added the following criteria to the label: in patients not treated with chemotherapy, there is no indication for the use of ESAs and there might be an increased risk of death when ESAs are administered to a target of 12–14 g/dl; in people treated with curative intent, ESAs should be used with caution.

Current evidence

Previous guidance (TA142) was based on evidence presented by Wilson and colleagues (2007) as part of the Health Technology Assessment (HTA) process. This review had a wider focus than the present HTA in that it considered the use of ESAs with regard to their effectiveness in treating cancer-related anaemia, irrespective of whether it was caused by cancer treatment.

Scoping searches identified two relevant recent Cochrane reviews (Tonia T, Mettler A, Robert N, Schwarzer G, Seidenfeld J, Weingart O, *et al.* Erythropoietin or darbepoetin for patients with cancer. *Cochrane Database Syst Rev* 2012;**12**:CD003407; Bohlius J, Schmidlin K, Brillant C, Schwarzer G, Trelle S, Seidenfeld J, *et al.* Erythropoietin or Darbepoetin for patients with cancer – meta-analysis based on individual patient data. *Cochrane Database Syst Rev* 2009;**3**:CD007303). As in the study by Wilson and colleagues (2007), the focus of these reviews was the use of ESAs with regard to their effectiveness in treating cancer-related anaemia, irrespective of whether it was caused by cancer treatment.

Current evidence suggests that ESAs reduce the need for RBCT but increase the risk of thromboembolic events and deaths. There is suggestive evidence that ESAs may improve quality of life. Whether and how ESAs affect tumour control remains uncertain.

Objective

The following question was addressed by this report: 'What is the effectiveness and cost-effectiveness of ESAs in anaemia associated with cancer treatment (specifically chemotherapy)?'

The review was based on a predefined scope issued by NICE and was conducted in accordance with a predefined protocol. Given the publication of the 2012 Cochrane review (Tonia and colleagues 2012) and the fact that no studies were completely aligned with current UK authorisation, studies were considered eligible for inclusion in accordance with UK marketing authorisations if they used a licensed starting dose, irrespective of how they dealt with other criteria stipulated by the licence.

The ESAs considered were epoetin alfa (Eprex®, Janssen-Cilag Ltd and Binocrit®, Sandoz Ltd); epoetin beta (NeoRecormon®, Roche Products Ltd); epoetin theta (Eporatio®, Teva Pharmaceuticals Ltd); epoetin zeta (Retacrit®, Hospira UK Ltd) and darbepoetin alfa (Aranesp®, Amgen Inc.). All interventions were considered only according to their UK marketing authorisation. The key assumption maintained throughout this report is that all ESAs are equally effective.

Methods

Clinical effectiveness

The search strategy is based on the strategy used in the previous HTA review on this topic (Wilson and colleagues 2007). The databases searched included The Cochrane Library, MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE, Web of Science, Cumulative Index to Nursing and Allied Health Literature (CINAHL), British Nursing Index, Health Management Information Consortium, Current Controlled Trials and ClinicalTrials.gov. The US Food and Drug Administration and EMA websites were also searched. As this is an update of a previous review, databases were searched from 2004 to 2013. Search filters were applied to retrieve randomised controlled trials (RCTs) and quality-of-life studies. Bibliographies of included papers were scrutinised for further potentially includable studies. The reference lists of the industry submissions were also scrutinised for additional studies. Because of resource limitations, the search was restricted to English-language papers only. All references were managed using EndNote X5 (Thomson Reuters, CA, USA) and Microsoft Excel 2010 (Microsoft Corporation, Redmond, WA, USA) software.

Titles and abstracts returned by the search strategy were examined independently by four researchers and screened for possible inclusion. Disagreements were resolved by discussion. Full texts of the identified studies were obtained and examined independently for inclusion or exclusion and disagreements were again resolved by discussion. Included studies from the previous HTA review (Wilson and colleagues 2007) were also screened for inclusion by two researchers. Eligibility criteria were as follows:

- population: people with CIA
- intervention: ESAs (epoetin alfa, beta, theta and zeta and darbepoetin alfa) with starting doses according to European labelling
- comparator: best supportive care, defined as adjusting cancer treatment, RBCT and iron supplementation
- outcomes: Hb increase, RBCT requirement, overall survival (OS), adverse events (AEs) (thromboembolic events, hypertension, pruritus and seizures) and HRQoL
- study design: RCTs.

Data were extracted by one reviewer and checked by another. Disagreements were resolved by discussion.

The results of individual trials were pooled using meta-analysis when possible and justified. A random-effects model was assumed for all meta-analyses. When data were not reported in the published papers they were extracted from the 2012 Cochrane review (Tonia and colleagues 2012). This was justified on the basis that the Cochrane review authors had had access to additional unpublished materials when conducting their review. When meta-analysis was not possible narrative synthesis, supported by information collected in the data extraction tables, was used to summarise the evidence base.

Subgroup analyses were conducted: mean Hb level at baseline (< 10 g/dl, < 11 g/dl, < 12 g/dl, < 14.5 g/dl, not reported); Hb inclusion criteria (≤ 11 g/dl and > 11 g/dl); malignancy type (solid, haematological, mixed, not reported); ovarian cancer; chemotherapy type (platinum, non-platinum, chemotherapy plus radiotherapy, mixed chemotherapy, not reported); ESA type (short lasting, long lasting); iron supplementation (given, not given, given differently in treatment arm, not reported); duration of ESA medication (6–9 weeks, 12–16 weeks, 17–20 weeks, > 20 weeks); and study design [blinded (RCT), unblinded (randomised open label)]. In addition,

we also conducted post-hoc analyses considering inclusion Hb level closer to licence (≤ 11 g/dl and > 11 g/dl) and target Hb level closer to licence (≤ 13 g/dl and > 13 g/dl).

Cost-effectiveness review of past economic evaluations

The previous NICE appraisal (TA142) by Wilson and colleagues (2007) included a systematic review of published evidence of the cost-effectiveness of ESAs for CIA. Several databases (including MEDLINE and EMBASE) were searched, resulting in 491 records being identified. After screening by title and abstract, 44 full-text articles were retrieved for assessment. Five studies were eligible for inclusion and were critically appraised and summarised. Of these five studies, three were cost–utility analyses [i.e. studies reporting costs and quality-adjusted life-years (QALYs)].

We undertook to update the systematic review to identify any evidence regarding the cost–utility of ESAs, particularly with relevance to the NHS. ESA administration was considered within licence for inclusion in this review, based on dose frequency but not dose quantity (i.e. once weekly for any ESA, three times a week for epoetin alfa and epoetin zeta, once every 3 weeks for darbepoetin alfa and three to seven times weekly for epoetin beta). Fixed and weight-based dosages were allowed.

Searches were conducted in several databases (including MEDLINE and EMBASE), with the results limited to studies published since 2004 when possible, resulting in 1163 records being identified. Following removal of duplicate records, 843 titles and abstracts were screened independently by two reviewers. Fifty-four full-text articles were assessed for eligibility and 29 were judged to be eligible. Five studies were excluded as they were multiple publications, meaning that 24 studies were included.

Peninsula Technology Assessment Group cost–utility model

Model structure

In the Peninsula Technology Assessment Group (PenTAG) assessment, the model took the form of a simple, empirical model, informed directly by the systematic review of clinical effectiveness. The model compared patients receiving ESA therapy with patients not receiving ESA therapy and was split into two temporal sections, one to evaluate the short-term costs and QALYs (while patients are anaemic) and one to evaluate long-term QALYs.

Short-term costs were accrued in the form of ESA drug acquisition and administration, RBCT costs and costs of adverse events. Cancer costs were assumed to be equal for all patients. No difference in survival time in the short term was modelled between arms. Long-term costs were not modelled because of the uncertainty of such costs given the varied patient population and to avoid an arbitrary value disadvantaging a strategy with a survival benefit.

Short-term QALYs are accrued as the utility associated with empirical observation of Hb over time. Here, Hb levels over time were taken directly from clinical trials and this approach attempted to bolt on an economic evaluation to the RCTs of ESAs. The short-term QALY gain included time receiving ESA therapy and a time post-ESA therapy called normalisation, when patients return to their ‘normal’ Hb level (in the base case this is set to 12 g/dl).

Long-term QALYs are accrued because of potential differences in OS between the two arms. These are calculated by estimating OS in each arm and applying a long-term utility common to both arms; that is, it is assumed that long-term QALY differences come about only through a difference in survival as a result of ESA therapy, not through any enduring impact on HRQoL.

An exponential distribution was assumed for OS of patients not receiving ESA therapy in the base case, as this is consistent with results from a number of trials. A hazard ratio (HR) was applied to OS for lifetime for patients receiving ESA therapy. Alternative modelling assumptions were explored through scenario analyses.

Model parameters

On recommendation from NICE and in keeping with the clinical effectiveness review, equal effectiveness was assumed for ESAs. However, some parameters specific to each ESA, such as drug doses and costs, were varied between ESAs.

To ensure consistency between costs and benefits, all parameters were estimated on an intention-to-treat basis. For example, we used the mean weekly dosage of ESAs averaged over all patients at baseline for the full intended treatment duration. This average includes some patients who withdraw from ESA treatment during the trial.

Clinical effectiveness

Most parameters were estimated from outcomes reported by randomised trials included in the systematic review of clinical effectiveness. No evidence from RCTs was found for normalisation of Hb levels following chemotherapy cessation and so this part of the model had to be parameterised on the basis of clinical expert opinion.

Utilities

For the analysis, the model required two sources of utility values: (1) utility as a function of Hb levels during ESA treatment and during normalisation to reflect the impact of ESAs on HRQoL and (2) a constant utility value after normalisation, equal in all treatment arms.

A review was conducted of studies for (1) and a single study was chosen, from which the PenTAG base case was calculated (Harrow BS, Eaton CB, Roberts MB, Assaf AR, Luo X, Chen Z. Health utilities associated with hemoglobin levels and blood loss in postmenopausal women: the Women's Health Initiative. *Value Health* 2011;**14**:555–63) and scaled to the European Quality of Life-5 Dimensions (EQ-5D), giving a 0.028 increase in utility per unit increase for Hb. The long-term utility (2) was calculated using an estimate for cancer utility from Tengs and Wallace (Tengs TO, Wallace A. One thousand health-related quality-of-life estimates. *Med Care* 2000;**38**:583–637) and applying the age-related utility calculated from Ara and Brazier (Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. *Value Health* 2010;**13**:509–18). This gave a utility of 0.76.

We did not explicitly model disutility from adverse events because of a lack of data.

Costs

In this analysis we modelled the following costs: blood test costs, ESA prices, RBCT costs (unit cost of blood and cost of transfusion appointment) and costs of adverse events. We did not model long-term costs in the base case given the uncertainty attached to these values as a result of the wide patient population. We assumed that the cost of intravenous iron supplementation could be ignored, as it will be very similar for all arms. Costs were adjusted to 2014/15 prices when appropriate.

Base-case ESA costs were taken from the *British National Formulary* (Joint Formulary Committee. *British National Formulary*. 66th ed. London: BMJ Group and Pharmaceutical Press; 2013). Wholesale acquisition costs for ESAs were also obtained and used in a scenario analysis. ESAs were assumed to be administered once weekly in the base case, by a mixture of general practitioners, district hospital staff nurses and self-administration. ESAs were also assumed to incur costs for four additional blood tests compared with the no ESA arm, in line with the possibility that additional blood tests would continue post chemotherapy for those patients on ESAs.

The adverse events that we accounted for in this cost-effectiveness analysis were identified through the clinical effectiveness review. In particular, we accounted for the cost of thromboembolic events, hypertension and thrombocytopenia. The unit costs of managing thromboembolic events (particularly pulmonary embolism and deep-vein thrombosis), hypertension and thrombocytopenia were identified

through NHS reference costs 2012–13 [Department of Health. *Reference Costs 2012–13*. London: Department of Health; 2013. URL: www.gov.uk/government/uploads/system/uploads/attachment_data/file/260403/nhs_reference_costs_2012–13.pdf (accessed16 June 2015)].

Unit costs for the supply of RBCs were taken directly from NHS Blood and Transplant 2012/13 costs (£122 per unit) [see www.nhsbt.nhs.uk/annualreview/blood-supply/ (accessed July 2015)] and unit costs of a transfusion appointment were calculated using figures reported in Varney and Guest (Varney SJ, Guest JF. The annual cost of blood transfusions in the UK. *Transfus Med* 2003;**13**:205–18).

Other model characteristics

A lifetime time horizon was used in the model. The perspective adopted was that of the NHS and Personal Social Services. Costs and benefits were discounted at 3.5% per annum.

The age and weight of patients in the model were estimated from the age and weight reported in clinical studies included in the systematic review of clinical effectiveness evidence.

Results

Clinical effectiveness

Number and quality of effectiveness studies

A total of 2376 titles/abstracts were identified through database searching from 2004 to 2013. Of 1515 titles and abstracts screened (including 1404 titles/abstracts identified via the PenTAG searches), 23 RCTs (reported in 34 publications) were found that matched the inclusion criteria for this review. All of the included studies had been included in the recent Cochrane review (Tonia and colleagues 2012). The PenTAG review included one full paper (Moebus V, Jackisch C, Schneeweiss A, Huober J, Lueck HJ, du Bois A, *et al.* Adding epoetin alfa to intense dose-dense adjuvant chemotherapy for breast cancer: randomized clinical trial. *J Natl Cancer Inst* 2013;**105**:1018–26) which reported a study for which only an earlier abstract [Moebus V, Lueck H, Thomssen C, Harbeck N, Nitz U, Kreienberg R, *et al.* The impact of epoetin-alpha on anemia, red blood cell (RBC) transfusions, and survival in breast cancer patients (pts) treated with dose-dense sequential chemotherapy: mature results of an AGO Phase III study (ETC trial). *J Clin Oncol* 2007;**25**:S569] was included in the Cochrane review (Tonia and colleagues 2012). Thirteen studies compared ESAs plus supportive care for anaemia (including transfusions) with placebo plus supportive care for anaemia (including transfusions) alone and 10 studies compared ESAs plus supportive care for anaemia (including transfusions) with supportive care for anaemia (including transfusions) alone. Of note, none of the included studies evaluated ESAs entirely within the remit of their marketing authorisations; in particular, start and target Hb levels and stopping rules were all generally higher than specified in the licence.

Taken as a whole, the quality of the trials was moderate to poor. For most of the trials it was difficult to make a general assessment of study quality because of reporting omissions. Most notably, all trials lacked clarity in the reporting of allocation methods (the procedure for randomisation and/or allocation concealment).

Assessment of effectiveness

Overall, the analysis of haematological response (defined as an improvement in Hb of 2 g/dl or a 6% increase in haematocrit level) included 10 studies with 2228 participants. Meta-analysis showed a statistically significant difference in Hb response in favour of treatment [risk ratio (RR) 3.29, 95% confidence interval (CI) 2.84 to 3.81]. In total, 63% (759/1213) of participants who received ESAs achieved a haematological response, compared with 18% (182/1015) of participants who did not. Subgroup analyses were inconclusive. Treatment with ESAs reduced the number of patients receiving RBCTs by an estimated 37%. These estimates are consistent with previously reported estimates.

The results of previous reviews with respect to survival have varied and there is much debate surrounding the impact of ESAs on survival. Survival data were available from 21 trials including 5054 participants. The HR for survival was 0.97 (95% CI 0.83 to 1.13); the forest plot suggested that there was a tendency for smaller studies to favour ESA treatment. Although this estimate differed from those reported by Wilson and colleagues (2007) and Tonia and colleagues (2012) (1.05, 95% CI 1.00 to 1.11, and 1.03, 95% CI 0.83 to 1.13, respectively), there was considerable uncertainty around this estimate and statistically significant heterogeneity was identified ($I^2 = 42.4\%$; $\chi^2 = 29.5$, degrees of freedom = 17; $p = 0.03$). In addition, subgroup analyses did not identify groups at lower or higher risk.

On-study mortality was defined as death occurring up to 30 days after the active study period. Data, extracted from the Cochrane review (Tonia and colleagues 2012), were available from 21 studies including 5085 participants. Analyses suggested that treatment with ESAs in patients with CIA did not have a statistically significant effect on mortality (HR 0.86, 95% CI 0.67 to 1.11). In total, 11% (174/1586) of participants who received ESAs had died within 30 days of the active study period, compared with 12% (164/1381) of patients in the control groups.

All AEs were relatively rare compared with the other outcomes considered in this report. The AE with the highest rate was thrombocytopenia/haemorrhage [6% (55/877) in the ESA treatment groups and 6% (54/838) in the control groups]. The summary estimate for thrombocytopenia/haemorrhage in the PenTAG review was RR 0.93 (95% CI 0.65 to 1.34), compared with RR 1.21 (95% CI 1.04 to 1.42) in the Cochrane review (Tonia and colleagues 2012). However, although the point estimate is lower compared with previous results, the data are insufficient to rule out detrimental effects. Overall, the data suggest that treatment with ESAs in patients with CIA increases the risk for thromboembolic events (RR 1.46, 95% CI 1.08 to 1.99), increases the number of hypertension events (RR 1.80, 95% CI 1.14 to 2.85), increases the number of cases of pruritus (RR 2.04, 95% CI 1.11 to 3.75) (skin rash, irritation and pruritus were combined in the analyses) and results in a non-significant increase in the number of seizures (RR of 1.19, 95% CI 0.33 to 4.38), consistent with previous estimates.

Subgroup analyses

Two of the subgroups evaluated corresponded with the current NICE recommendations: women with ovarian cancer receiving platinum-based chemotherapy and people unable to receive a blood transfusion.

One trial (ten Bokkel Huinink WW, de Swart CA, van Toorn DW, Morack G, Breed WP, Hillen HF, *et al.* Controlled multicentre study of the influence of subcutaneous recombinant human erythropoietin on anaemia and transfusion dependency in patients with ovarian carcinoma treated with platinum-based chemotherapy. *Med Oncol* 1998;**15**:174–82) evaluated the use of ESAs in women with ovarian cancer. The data confirm the results from previous analyses with respect to anaemia-related outcomes; that is, improvements in haematological response and a reduction in RBCT requirement, but an increased risk for thromboembolic events in the ESA treatment group. OS was not measured. No trials were identified that evaluated people unable to receive RBCTs. However, it is reasonable to assume that ESAs are likely to be effective in improving the Hb level in this subpopulation.

In addition, subgroup analyses considering any type of cancer and platinum-based chemotherapy, platinum-based chemotherapy in head and neck malignancies and iron supplementation were conducted.

Other factors for consideration

As previously stated, studies were eligible for inclusion in the systematic review if they used a licensed starting dose, irrespective of how they dealt with other criteria stipulated by the licence. In addition to dose, we also assessed the impact of inclusion Hb level (≤ 11 g/dl vs. > 11 g/dl) and target Hb level (≤ 13 g/dl vs. > 13 g/dl) in post-hoc subgroup analyses.

A trend associated with the administration of ESAs according to licence recommendations was noticed. It appeared that effectiveness in terms of some outcomes was improved when ESAs were evaluated closer to their licensed indications, for example dose and inclusion Hb level (≤ 11 g/dl) and dose, inclusion Hb level (≤ 11 g/dl) and target Hb level (≤ 13 g/dl). Findings for anaemia-related outcomes showed improvements consistent with previous analyses. The effectiveness with regard to malignancy-related outcomes did appear to be affected by the licence application, and estimated effects of ESAs administered in accordance with licence recommendations were notably lower than those reported in previous analyses. Importantly, although the results for thromboembolic events from the PenTAG review agree with those in the Cochrane review (Tonia and colleagues 2012), suggesting an increase in thromboembolic events in patients in the ESA groups compared with the control groups, the closer the studies were to the licence recommendations the smaller the point estimates were (suggesting less detrimental effects of ESA).

However, all subgroup analyses must be interpreted with caution. The number of studies per subgroup is small and the CIs remain wide. The analyses may not have statistical power to detect the effects of the licence application on the effectiveness of outcomes, if such effects exist. Furthermore, we have not sought to address multiple testing issues that arise when considering subgroups, and so the statistical significance of the results may appear overstated.

Health-related quality of life

Thirteen trials measuring HRQoL were reported in 23 publications. Of these publications, 11 primary studies were included in the review by Wilson and colleagues (2007). Three new primary studies were identified in the update searches.

Taken as a whole, the quality of the trials was moderate to poor. For most of the trials it was difficult to make a general assessment about study quality because of reporting omissions. Baseline characteristics were unbalanced in two trials. Patients and physicians were blinded for the majority of trials, which is considered to have a significant impact on HRQoL assessed by self-reporting. Significant patient numbers were lost to follow-up for HRQoL outcomes in at least six trials.

Given the variability of reporting in the published papers, data for the Functional Assessment of Cancer Therapy – Fatigue (FACT-F) subscale, consisting of 13 specific items (score 0–52), were extracted from the Cochrane review by Tonia and colleagues (2012) for use in the PenTAG analyses. FACT-F scores were available from seven studies, with one new primary study identified. Overall, the conclusions from the PenTAG review were in agreement with those of the Cochrane review (Tonia and colleagues 2012), in that there was a statistically significant difference between patients treated with ESAs and control subjects when combining HRQoL parameters. However, the pooled mean difference between the treatment arm and the control arm was < 3 units, which is not considered clinically significant for FACT-F. Univariate subgroup analyses conducted for FACT-F outcomes according to chemotherapy type, malignancy type, intervention (epoetin or darbepoetin) and study duration also showed similarly statistically significant differences between the treatment arm and the control arm.

Meta-analysis was performed on Functional Assessment of Cancer Therapy – General and Functional Assessment of Cancer Therapy – Anaemia (seven items) data; however, only three studies were suitable for inclusion for each scale and their results displayed high levels of heterogeneity. The result of no statistical difference between the intervention arm and the control arm must therefore be treated with caution.

Overall, conclusions from the PenTAG review are in agreement with those from the Cochrane review (Tonia and colleagues 2012) and the previous HTA review (Wilson and colleagues 2007). We have attempted to include populations closer to the licence for ESAs to understand the effects on HRQoL at these doses. Furthermore, as the previous HTA (Wilson and colleagues 2007) was able to use only a vote-counting method to estimate the positive direction of effect, the results from the PenTAG review have been quantified and pooled to enable a more direct comparison between treatments.

Cost-effectiveness

Published economic evaluations

Of the 24 included studies, 12 were abstracts only. Two related to the previous NICE appraisal, three were new cost–utility studies (Fagnoni P, Limat S, Chaigneau L, Guardiola E, Briaud S, Schmitt B, *et al.* Clinical and economic impact of epoetin in adjuvant-chemotherapy for breast cancer. *Support Care Cancer* 2006;**14**:1030–7; Borg S, Glenngard AH, Österborg A, Persson U. The cost-effectiveness of treatment with erythropoietin compared to red blood cell transfusions for patients with chemotherapy induced anaemia: a Markov model. *Acta Oncol* 2008;**47**:1009–17; Tonelli and colleagues 2009) and two were or included new systematic reviews (Duh MS, Weiner JR, White LA, Lefebvre P, Greenberg PE. Management of anaemia: a critical and systematic review of the cost effectiveness of erythropoiesis-stimulating agents. *Pharmacoeconomics* 2008;**26**:99–120; Tonelli and colleagues 2009).

Data extraction was conducted for all 24 included studies, but attention was focused on the new cost–utility studies and new systematic reviews. New cost–utility studies were critically appraised using quality assessment tools [either the Evers checklist (Evers S, Goossens M, de Vet H, van Tulder M, Ament A. Criteria list for assessment of methodological quality of economic evaluations: Consensus on Health Economic Criteria. *Int J Technol Assess Health Care* 2005;**21**:240–5) or the Philips checklist (Philips Z, Bojke L, Sculpher M, Claxton K, Golder S. Good practice guidelines for decision-analytic modelling in health technology assessment: a review and consolidation of quality assessment. *Pharmacoeconomics* 2006;**24**:355–71), as appropriate]. Narrative synthesis was conducted.

All of the studies (pooling those included from the previous review and the new studies) finding favourable cost-effectiveness for ESAs were funded or conducted by industry. Many of these assumed that ESA therapy would lead to a survival benefit for patients, although this is not supported by recent systematic reviews and meta-analyses.

A key assumption in almost all analyses was that raising Hb levels would improve HRQoL, although in no case was this assumption based on published RCT evidence using a preference-based quality-of-life measure.

A number of studies assumed a period following the end of chemotherapy treatment during which Hb levels would gradually return to normal (termed normalisation) and participants in the ESA arm would continue to accrue incremental benefits in quality of life over participants in the no ESA arm; to our knowledge, no evidence for or against normalisation has been presented in the published literature.

In the absence of survival benefit the expected health gain from ESA therapy is small (up to 0.035 QALYs) and is subject to uncertainty.

Studies did not incorporate current list prices or wholesale acquisition costs, which could significantly reduce the drug acquisition component of the cost of ESA therapy and improve cost-effectiveness.

There is a need for an up-to-date analysis of the cost-effectiveness of ESAs in the NHS to reflect reduced drug acquisition costs, changes to licences and market entry of additional comparators. This analysis will need to explore the significant amount of uncertainty that still remains.

Appraisal of industry submissions

Six manufacturer submissions were potentially available for this multiple technology appraisal. However, no manufacturers submitted an economic evaluation.

Peninsula Technology Assessment Group model

Base case

We found that the deterministic base case had incremental cost-effectiveness ratios (ICERs) for ESA treatment compared with no ESA treatment from £19,429 to £35,018 per QALY gained. Given that this covers a wide range of values and the entirety of the £20,000–30,000 per QALY range that is often used as a cost-effectiveness threshold by NICE, it was considered appropriate to emphasise the results of the probabilistic sensitivity analysis (PSA).

Sensitivity analyses

The expected mean results from the PSA gave ICERs that were lower than those in the deterministic base case (£14,724–£27,226 per QALY gained). On average, 0.092 (95% CI of –0.264 to 0.447) QALYs were gained for ESA treatment compared with no ESA treatment. The incremental costs for the most cost-effective ESA [Binocrit (epoetin alfa)] were £1349 (95% CI £710 to £1987). The ICER for Binocrit had a 95% credible interval (CrI) that was dominated by no ESA use (fewer QALYs and higher costs) at its upper end, with a lower value of £2350 per QALY gained (rounded to the nearest £50). In 36% of simulations there was an OS loss, with 31.4% of simulations having an overall QALY loss. Given that this was the most cost-effective ESA treatment, it is unsurprising that the rest of the ESAs were also dominated at their upper CrI limit. These results suggest that ESAs may be cost-effective at a threshold of £20,000 per QALY, but this could also be a result of chance variation and there is a significant chance of QALY loss in patients receiving ESA therapy.

Scenario analyses

Scenario analyses were conducted to investigate what was driving the wide range of values in the ICER CrIs. The three considered most important were:

1. setting the OS HR to exactly 1, so that survival is the same for both patients on ESA therapy and patients not on ESA therapy
2. setting ESA costs to wholesale acquisition costs in an attempt to establish the real costs to the NHS
3. both setting the OS HR to exactly 1 and the ESA costs to wholesale acquisition costs.

In the first of these scenarios, in which survival is assumed to be equal for the two treatment arms, we found that the QALY gain was greatly reduced (0.014) (as well as the 95% CI 0.001 to 0.027), suggesting that much of the variability in the base-case QALYs comes from the QALYs accrued during long-term survival. The reduction in QALYs also increases the ICERs, with the most cost-effective ESA achieving an ICER of £96,754 per QALY gained (95% CrI £36,500 to > £300,000 per QALY gained) in the PSA. None of the CrIs for the ICERs fell below £30,000 per QALY gained, suggesting that in this scenario ESAs are unlikely to be cost-effective.

In the second scenario, in which wholesale acquisition costs were implemented, (commercial-in-confidence information has been removed) [for the least costly ESA: Retacrit (epoetin zeta)] per QALY gained. However, in this scenario the 95% CrI went from ESA dominating at one end (with more QALYs and lower costs than no ESA use) to ESA being dominated by the no ESA arm at the other end.

In the third scenario, in which survival is assumed to be equal for both treatment arms and wholesale acquisition costs are used (commercial-in-confidence information has been removed).

We also conducted scenario analyses on a subgroup of studies in which the initial Hb level for participants was ≤ 11 g/dl, as well as investigating the assumptions around OS. Univariate sensitivity analyses were also conducted. The uncertainties identified in the analyses of this subgroup of studies were less significant than those identified for the analyses of all studies (presented in the previous paragraphs).

Discussion

Strengths and limitations: clinical effectiveness and quality-of-life reviews

The overview of clinical effectiveness systematic reviews was conducted by an independent, experienced research team using the latest evidence and working to a prespecified protocol (PROSPERO CRD42013005812). This technology assessment builds on existing secondary research and economic evaluations. However, there are some important sources of uncertainty that impact on the conclusions:

- *Relative effectiveness*. We did not address the relative effectiveness of different ESAs. Lack of head-to-head RCT evidence would have been an important limitation if we had tried to do this.
- *Dose*. The protocol stated that ESAs should be evaluated in accordance with their UK marketing authorisations. However, given that no studies were completely aligned with the current UK marketing authorisation, we identified studies that were closest to the current UK marketing authorisation, focusing initially on the starting dose. It is important to note that beyond the start dose there were still significant differences from the current licence recommendations in the included studies. Also, we did not prespecify the criteria used to define 'closest to the current UK marketing authorisation', but we did explore alternative, stricter definitions.
- *Generalisability*. There may be other challenges to the applicability of the included trials, which were carried out up to 20 years ago. Chemotherapy has changed during this period, as has the quality of supportive treatment.
- *Study quality*. The included trials were of variable quality, but all were flawed to some degree. Most notably, all trials lacked clarity about randomisation and allocation concealment. The general problem of poor reporting of trials on this topic was greatly assisted by the recent Cochrane review (Tonia and colleagues 2012). The authors had gathered further information from investigators and manufacturers and this information was used in the meta-analysis for the current review.
- *Heterogeneity*. There is considerable unexplained statistical heterogeneity for a number of outcomes, particularly survival.
- *Publication bias*. There was some evidence in both the previous review (Wilson and colleagues 2007) and the Cochrane review (Tonia and colleagues 2012) that the results from small negative trials may not be available for inclusion in systematic reviews, suggesting the possibility of publication bias. For some outcomes in this review, for example HRQoL, this could not be further investigated because of the small number of included studies; for others, such as survival, there was continuing support for the possibility of publication bias. Industry-sponsored trials predominated.
- *Precision*. Although there is an apparent wealth of RCTs, only a minority of these were included because of the desire to address effectiveness as close as possible to current UK marketing authorisations. In consequence, the 95% CIs were often wide and included values indicating no difference in effect. In addition, it is not clear whether the total numbers of patients in the trials included were sufficient to establish the true presence or absence of an effect, either because events are uncommon, for example adverse events, or because the effect size that would be deemed to be clinically important is small, as would be the case with survival.
- *Multiple testing*. Although we were aware of the possibility of spuriously positive tests arising for statistical significance because of the multiple subgroup analyses carried out, we did not formally make adjustments for this.

The limitations identified impact on the key outcomes as follows:

- Haematological response and numbers transfused appear to be robust estimates, with no marked heterogeneity or subgroup effects.
- Hb change does show important heterogeneity, which may possibly indicate subgroup effects; however, analyses in this respect were inconclusive.
- HRQoL is affected by the variability of instruments used and study quality.
- Adverse events are mainly affected by the quality of information available, the variability in the definition of individual adverse events used and the width of the CIs.

- Survival is also subject to all of the limitations outlined above. Marked heterogeneity was identified for which no explanation could be provided. OS was defined as the longest follow-up available. This meant that there was a mix of studies with short- and long-term follow-up (i.e. OS effect estimates may be from different time points).

Strengths and limitations: systematic review of cost-effectiveness studies

The systematic review of cost-effectiveness evidence was conducted by an independent research team using the latest evidence and to a prespecified protocol. Two new systematic reviews were identified, neither of which identified studies that would have been eligible for this review.

Limitations were identified as follows:

- The searches were limited to English-language studies because of resource limitations.
- Only systematic reviews and cost–utility studies were fully critically appraised and considered in the narrative synthesis.
- Records from database searches published pre 2004 were excluded, although it was not possible to assess whether these had been screened for eligibility in the systematic review presented by Wilson and colleagues (2007). Studies using darbepoetin alfa once every 2 weeks were excluded as being out of licence, although these could have usefully contributed to the review.

Limitations: Peninsula Technology Assessment Group model

The main limitations of the updated model and its outputs are as follows:

- Despite being highly influential in terms of the model results, the marginally beneficial OS HR identified in the clinical effectiveness section has no strong biological rationale. Although many post-hoc suggestions have been advanced to try to explain both the increases and decreases in survival observed in individual ESA RCTs, most of these results can be explained by chance alone.
- The OS HR is applied on the assumption that proportional hazards apply for a lifetime after ESA therapy, although to our knowledge the proportional hazards assumption has not been tested. Most included studies had a limited follow-up period and so the long-term impact on survival is not well known. Limiting the effect of ESA therapy on survival to 3 years results in a significant worsening of the cost-effectiveness of ESAs.
- The mapping of Hb level to utility is a surrogate outcome with the problems that this entails. Furthermore, the utility identified for the base case was not ideal: it had to be additionally mapped to the EQ-5D and the patient population was cancer patients without ESA use only. The main weakness of the study design was that it was observational. This means that the estimated relationship between utility and Hb level may be biased because of unmeasured confounding variables and it is likely that this would bias the results in favour of the ESA arm compared with the control arm.
- Furthermore, evidence is lacking for the process of normalisation, this was entirely informed by clinical expert opinion.
- We also assumed constant cancer costs between the ESA arm and the no ESA arm; however, this may not be the case.
- The model assumes that there is no long-term cost difference between arms, but it does assume a long-term survival benefit for the ESA arm. As previous models indicated, this long-term aspect of the model is an area that has not been assessed in great detail before. As such, this is an area of which there needs to be better understanding.
- As the model is primarily driven by data from the clinical effectiveness review, the input parameters may not be in line with current practice. This also means that limitations of the clinical effectiveness review carry over to the cost-effectiveness results. Furthermore, the inherent uncertainty in the estimates from the clinical effectiveness meta-analysis and the associated limitations are a main source of uncertainty that occurs within the model. This also means that the effectiveness of the ESAs is assumed to be equal, as this follows from the clinical effectiveness review.

Conclusions

The previous HTA review (Wilson and colleagues 2007) concluded that:

> *Epo is effective in improving haematological response and reducing RBCT requirements. It also appears to improve HRQoL. Its impact on side-effects and survival remains highly uncertain. If there is no impact on survival, it seems highly unlikely that ESAs would be considered a cost-effective use of healthcare resources.*
>
> *p. iv*

Additional clinical effectiveness evidence identified in this updated systematic review continues to suggest that there is clinical benefit to be had from ESAs with respect to anaemia-related outcomes; that is, improvements in haematological response and a reduction in RBCT requirements. Data also suggest an improvement in HRQoL and this is better quantified than in the previous HTA review. The impact on side effects and survival, however, remains highly uncertain. Although the point estimates for both survival and thromboembolic events are lower than previously reported estimates, the 95% CIs are wide.

The conclusions concerning cost-effectiveness are also no clearer. Base-case ICERs for ESA treatment compared with no ESA treatment ranged from £19,429 to £35,018 per QALY gained, but sensitivity and scenario analyses demonstrate that there is considerable uncertainty in these results. In line with the previous HTA review, survival was an influential parameter. If the survival benefit reported in the clinical effectiveness review (0.97, 95% CI 0.83 to 1.13) is used, ESAs appear to be cost-effective on average, but this is highly uncertain and QALY loss cannot be ruled out (31.4% of simulations in the base case estimated a QALY loss from ESA therapy). However, if exactly equal survival is assumed regardless of ESA therapy, ESAs are predicted not to be cost-effective unless wholesale acquisition costs are used, in which case ESAs are predicted to be cost-effective on average, although approximately one in five simulations give an ICER of > £30,000 per QALY and approximately one in three simulations give an ICER of > £20,000 per QALY.

In summary, ESAs could be cost-effective, but there is considerable uncertainty in the results, mainly because of unknown impacts on OS.

Implications for service provision

- *Ongoing safety concerns*. When seeking clinical experts to advise us in this assessment we found that most relevant clinicians (i.e. oncologists, haematologists and gynaecologists) did not use ESA therapy in their clinical practice. This was generally because of concerns about safety and effectiveness (OS), as well as restrictions from previous NICE guidance (TA142).
- *Current usage*. It is difficult to assess how frequently ESA therapy is used within the indication of CIA because prescription records do not routinely link medication with indication and ESA therapy is widely used in individuals with chronic kidney disease (CKD). Some indirect evidence of the use of ESA therapy for CIA is available from the use of cost centres against which ESAs are recorded. Data analysed are suggestive of significant variability in current usage, consistent with the fact that many clinicians do not use ESAs because of safety concerns and current NICE guidance (TA142), although data quality is low and interpretation challenging.
- *Acquisition costs*. The costs at which hospitals acquire ESAs may be significantly lower than the list prices for these drugs. These prices are the subject of confidential negotiations and are commercially sensitive. At present, acquisition prices will largely be driven by demand for ESAs for individuals with CKD. Current prices could be amended if there are developments in the management of CKD or if demand for ESAs increases for patients with CIA (as might be expected following positive NICE guidance).

Suggested research priorities

- If ESAs are thought to have major potential for improving cancer care, large RCTs meeting current methods and reporting standards with adequate follow-up are needed to evaluate ESAs as administered in line with current marketing authorisations (including licence criteria for Hb levels).
- There should be improved estimates of the impact on tumour response and mortality; if these estimates are neutral or slightly beneficial it is plausible that ESAs could be cost-effective.
- There should be assessment of the frequency of the key potential adverse events related to ESA administration.
- More data are needed to assess the impact on HRQoL. These should include the effect on EQ-5D.
- More evidence is needed to assess the impact of Hb normalisation on utility.
- In addition to new trials, it may be valuable to revisit the Cochrane individual patient data meta-analysis and select studies that better fit 'licensed recommendations' with respect to Hb criteria and doses administered.
- It may also be helpful to explore reasons why an improvement in anaemia may lead to better outcomes; that is, whether ESAs allow better compliance with chemotherapy.

Study registration

This study is registered as PROSPERO CRD42013005812.

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