What is the clinical effectiveness of erythropoiesis stimulating agents for the treatment of cancer treatment-induced anaemia?

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INTRODUCTION

- Anaemia is a common condition in people with cancer. It is a side-effect of cancer treatment (chemotherapy-induced anaemia), or the disease itself [1]
- It is the most frequent haematological manifestation in people with cancer; >50% of people with cancer will be anaemic regardless of the treatment received; and approximately 20% of people undergoing chemotherapy will require red blood cell transfusion (RBCT)[1]
- Anaemia is associated with many symptoms including: dizziness, shortness of breath on exertion, palpitations, headache, and depression.[1] Severe fatigue is the most commonly reported symptom. All affect health-related quality of life[1]
- Cancer-treatment induced anaemia is typically managed by adjusting the cancer treatment regimen, giving iron supplements and, if anaemia is severe, blood transfusions[2,3]
- Erythropoiesis-stimulating agents (ESAs) (epoetin and darbepoetin) are licensed for use in conjunction with RBCT to improve cancer-treatment induced anaemia[4–9]

OBJECTIVE

- To review research evidence, to inform the National Institute for Health and Clinical Excellence (NICE) guidance to the National Health Service (NHS) in England and Wales, on the clinical effectiveness of ESAs for the treatment of cancer-treatment induced anaemia[10]

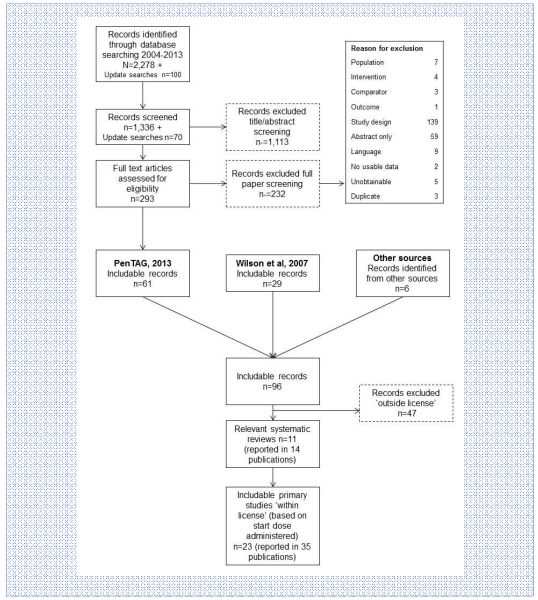
METHODS

- A systematic review of ESA studies evaluating starting doses according to European labelling was conducted according to published methodology (NHS Centre for Reviews and Dissemination)
- Electronic databases and grey literature sources were searched up to December 2013
- Eligibility criteria included:
  - **Population:** People with cancer-treatment induced anaemia
  - **Intervention**: ESAs (epoetin alfa, beta, theta and zeta; and, darbepoetin alfa) with starting doses according to European labelling
  - **Comparator:** Best supportive care (BSC); defined as adjusting cancer treatment; RBCT; and iron supplementation
  - **Outcomes:** Haemoglobin (Hb) increase; RBCT requirement; overall survival (OS); adverse events (AEs; thromboembolic events; hypertension; pruritus; and seizures); and, health-related quality of life (HRQoL)
  - **Study design:** Randomised controlled trials (RCTs)
- The methodological quality (risk for bias) of each study was assessed using modified Cochrane Risk of Bias criteria
- For all outcomes, statistical heterogeneity between the results of the studies was assessed by the degree of overlap between the 95% CIs from the different studies and by using the I^2 statistic
- Data were pooled where appropriate using random-effects meta-analyses

RESULTS

- Twenty-three RCTs were included in the review (**Figure 1**)

Figure 1. PRISMA flow diagram



- All studies used a licensed starting dose but other licence criteria e.g. inclusion and target Hb levels and stopping rules did not meet licence criteria and varied between studies
- Thirteen trials compared ESAs + standard care with placebo + standard care. The remaining 10 trials compared ESAs + standard care with standard care alone
- The quality of included trials was moderate or poor. For most of the trials it was difficult to make a general assessment about study quality due to reporting omissions.
- The age range of participants in the included trials was 18–92 years
- Participants had solid, haematological, or mixed malignancies; and the majority were treated with either received platinum- or non-platinum-based chemotherapy

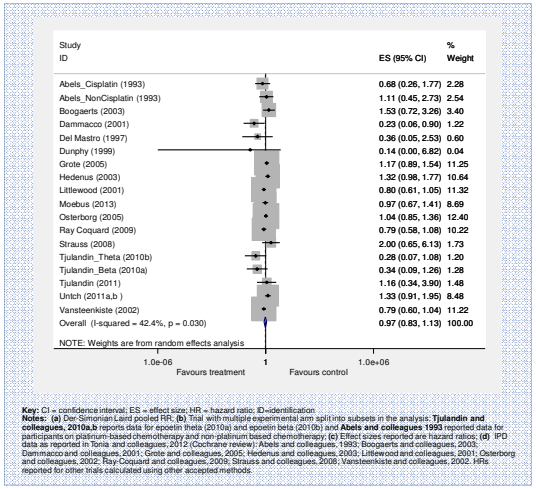
Table 1. Anaemia-related outcomes

Outcome	N Trials; participants	Results
Hb change	16 trials N=3,170	WMD 1.59 g/dl (95% CI 1.33, 1.84)
Haem response[a]	10 trials N=2,228)	RR 3.29 (95% CI 2.84, 3.81)
RBCT	22 trials N=4,779	RR 0.63 (95% CI 0.57, 0.69)
RBC units required	10 trials N=1,920	WMD -0.87 (95% CI -1.28, -0.46)

Key: CI = confidence interval; Haem = haematological; Hb = haemoglobin; RBC = red blood cell; RBCT = red blood cell requirement; RR = relative risk; WMD = weighted mean difference
Notes: (a) % with increase of ≥2 g/dl in Hb concentration, or increase of ≥26% in haematocrit

- Pooled estimates for anaemia-related outcomes (Hb change; haematological response; requirement for RBCT; units transfused) favoured ESA treatment (**Table 1**)
- ESA treatment was associated with a pooled risk ratio of 1.10 (95% CI 0.86 – 1.41) for complete tumour response (7 studies; n=1,909)
- Analyses suggest that treatment with ESAs did not have a significant effect on OS. Thirty five per cent (818/2,317) participants who received ESA s, and 35% (744/2,137) of participants in the control groups died. The risk of death was 0.97 (HR 0.97, 95% CI 0.83, 1.13) (**Figure 2**)
- Analyses suggest that treatment with ESAs did not have a significant effect on on-study mortality (defined as deaths occurring up to 30 days after the active study period). The risk ratio was 0.86 (95% CI 0.67 – 1.11) (21 studies; n=5,085)

Figure 2. Forest plot: Overall survival (random effects)



Key: CI = confidence interval; ES = effect size; HR = hazard ratio; ID=identification
Notes: (a) Der-Simonian Laird pooled HR; **(b)** Trial with multiple experimental arm split into subsets in the analysis: **Tjulandin and colleagues, 2010a,b** reports data for epoetin theta (2010a) and epoetin beta (2010b) and **Abels and colleagues 1993** reported data for participants on platinum-based chemotherapy and non-platinum based chemotherapy; **(c)** Effect sizes reported are hazard ratios; **(d)** IPD data as reported in Tonia and colleagues 2012 (Cochrane review): Abels and colleagues, 1993; Boogaerts and colleagues, 2003; Dammacco and colleagues, 2001; Grote and colleagues, 2005; Hedenus and colleagues, 2003; Littlewood and colleagues, 2001; Osterborg and colleagues, 2002; Ray-Coquard and colleagues, 2009; Strauss and colleagues, 2008; Vansteenkiste and colleagues, 2002. HRs reported for other trials calculated using other accepted methods.

- Although all AEs were relatively rare (max. 6%), an increased risk for thromboembolic events, pruritus and hypertension was found (**Table 2**)
- Data suggest an improvement in HRQoL (**Table 3**) although this is not considered clinically meaningful

Table 2. Safety-related outcomes

	Relative risk	Confidence interval
Thromboembolic events (14 trials; n=4,023)	1.46	1.07–1.99
Hypertension (9 trials; n=2,032)	1.80	1.14–2.85
Pruritus (7 trials; n=1,715)	2.04	1.11–3.75
Seizures (1 trial; n=289)	1.19	0.33–4.38
Thrombocytopenia & haemorrhage (6 trials; n=869)	0.93	0.65–1.34

Table 3. Health-related quality of life outcomes

	WMD	Confidence interval
FACT-Fatigue 7 trials; n=1,794	2.54	1.42 – 3.65
FACT-General 3 trials; n=686	2.98	-0.83 – 6.78
FACT-Anaemia 3 trials; n=686	2.60	-0.52 – 5.72

Key: FACT – Functional Assessment of Cancer Therapy; WMD – weighted mean difference

Subgroup & Sensitivity Analyses

- Subgroup analyses suggested a benefit for participants receiving platinum-based chemotherapy (HR 0.67 [95% CI 0.46 – 0.98]; 5 trials; n=1,119)
- Post-hoc sensitivity analyses of ESAs used 'closer to licence' (starting dose + starting Hb level ≤11 g/dl; and, starting dose + starting Hb level ≤11 g/dl + target Hb level ≤13 g/dl), also suggested a benefit HR 0.91 (95% CI 0.70 – 1.20; 10 studies), and HR 0.50 (95% CI: 0.20– 1.23; 3 studies), respectively. However, these estimates should be interpreted with caution as they are subject to uncertainty

CONCLUSIONS

- **Evidence suggests clinical benefit from ESAs with respect to anaemia-related outcomes**
- **The impact of ESAs on side-effects and survival is highly uncertain**
- **Good-quality, reliable data from trials of ESAs are lacking**
- **The uncertainty surrounding survival has implications for the cost-effectiveness of ESAs (see poster 1038PD)**

IMPLICATIONS FOR FURTHER RESEARCH

- **Further investigation of OS seems necessary. Long-term follow-up RCT evidence would be the ideal, but further research into the available evidence (see poster 1502P)**

LIMITATIONS

- The relative effectiveness of ESAs was not addressed; all ESAs were assumed to have equivalent efficacy
- No studies were completely aligned with their European labelling beyond the starting dose evaluated
- Questionable generalisability of trials published >20 years ago; chemotherapy has changed as has the quality of supportive treatment
- Trial quality was moderate or poor, although the general problem of poor reporting was greatly assisted by the recent Cochrane review (Tonia and colleagues, 2012[11])
- There was considerable unexplained heterogeneity for a number of outcomes particularly survival, and evidence of publication bias
- Adjustments were not made to account for multiple testing

REFERENCES

1. Mercadante et al., Cancer Treat Rev. 2000; 2. Schrijvers et al., Ann Oncol, 2010; 3. National Institute for Health and Clinical Excellence, Technology Appraisal 142, London: NICE, 2008; 4. Janssen-Cilag, SmPC, 2012; 5. Sandoz Ltd, SmPC, 2012; 6. Hospira UK Ltd, SmPC, 2012; 7. Roche Products Ltd, SmPC, 2012; 8. Teva Pharmaceuticals Ltd, SmPC, 2012; 9. Amgen Ltd, SmPC, 2012; 10. National Institute for Health and Clinical Excellence, Final Scope, London: NICE, 2013; 11. Tonia et al. Cochrane Database Syst Rev. 2012

DISCLOSURES

This project was commissioned by the NIHR HTA Programme.

ASSOCIATED POSTERS

1038P: *A cost-effectiveness analysis of erythropoiesis-stimulating agents for treating cancer-treatment induced anaemia. Huxley N, Snowsill T, Hoyle M, Crathorne L, Haasova M, Briscoe S, Coelho H, Medina-Lara M, Mujica Mota R, Napier M, Hyde C.*

1502P: *What is the clinical and cost effectiveness of erythropoietin-stimulating agents for the treatment of patients with cancer-treatment induced anaemia? Insights from cumulative meta-analyses (CMA) and lessons for cost-effectiveness analyses. Haasova M, Huxley N, Crathorne L, Hyde C.*

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