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A Targeted Literature Review of the Cost-Effectiveness of Erythropoiesis-Stimulating Agents as Standard Care for the Treatment of Chemotherapy-Induced Anemia

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INTRODUCTION

- Chemotherapy remains a core cancer treatment[1] for a range of malignancies (such as non-myeloid cancer); however, it is also associated with an array of adverse effects, including chemotherapy-induced anemia (CIA)[2]
  - CIA is an outcome of the treatment of malignant invasion of normal tissue, which leads to blood loss, bone marrow infiltration with disruption of erythropoiesis, and functional iron deficiency due to inflammation[2]
  - CIA is estimated to affect up to 75% of patients with cancer receiving chemotherapy, although prevalence varies according to treatment type[3]
- Historically, red blood cell transfusions have been used to effectively manage CIA, through the replacement of depleted hemoglobin. However, the effect of transfusions on anemia-related symptoms are short-lived and transfusions have been shown to increase the risk of venous and arterial thrombotic events and mortality in hospitalized patients with cancer[4,5]
- Several erythropoiesis-stimulating agents (ESAs) have demonstrated clinical efficacy for the treatment of CIA according to the UK National Institute for Health and Care Excellence; however, ESAs have also been associated with adverse events and may increase the risk for thromboembolic events and death[6–8]
- There is very limited information available on the cost-effectiveness of the ESA erythropoietin (EPO) for the treatment of CIA[9]

Objective

- **To assess published cost-effectiveness analyses using ESAs as standard care (SoC) for the treatment of CIA in non-myeloid cancers**

METHODS

- A targeted literature review was undertaken to identify and select economic evaluation models assessing the use of ESAs for the treatment of CIA in non-myeloid cancer in adult patients aged ≥18 years
- Five databases (MEDLINE, Embase, Health Technology Assessment Database, NHS Economic Evaluation Database and the Cost Effectiveness Analysis Registry), and three websites (European Medicines Agency [medicines only], National Institute for Health and Care Excellence, and the Institute for Clinical and Economic Review) were searched to identify studies reporting economic evaluations
- Reference lists of retrieved relevant systematic reviews published from 2015 to 2020 were also checked for eligible studies
  - Two reviewers independently assessed the records based on the title and abstract, and then on the full document
  - One reviewer extracted data from each cost-utility study, and a second reviewer checked the extracted data
  - The study findings were summarized and risk of bias was evaluated using the 36-point Drummond and Jefferson criteria[10]
  - Other non-cost-utility economic evaluation studies were also listed

RESULTS

- Data from nine cost-utility studies were included (three from the UK, one each from the USA, Canada, Thailand, France, Sweden, and one unconfirmed location) comparing ESAs (epoetin-alfa, -beta, -zeta or darbepoetin alfa, supplemented with blood transfusions as necessary) to blood transfusions with no ESAs/placebo, as SoC for CIA[9–20]
- Considerable study heterogeneity existed[9–20]
  - Economic model structures included decision tree (n=2), Markov (n=3), or cost integration with trial data/medical records (n=5)
  - Time horizons ranged from 15 weeks to lifetime
  - Seven studies included a heterogeneous cancer population, while two studies included breast cancer only
  - Various methods were used to assess health-related quality of life (HRQoL)
- Three studies identified recombinant human erythropoietin (rHuEPO) as being more cost-effective than blood transfusions alone as SoC, with incremental cost-effectiveness ratios estimated to be at or below the country's accepted cost-effectiveness threshold (**Table 1**)[9,14,15]

References

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RESULTS (continued)

Table 1. Summary of cost-utility analyses – Outcomes, cancer type and treatment

Study [Country]	Comparator	Effectiveness outcomes	Total costs	Incremental analyses	Other outcomes	Cancer type	Chemotherapy treatment*
Barosi 1998[11] [Unconfirmed - potentially Italy]	Conventional treatment with RBC transfusions alone	Base case with all chemo Quality-adjusted life expectancy increase by 8.4 days: 0.023 QALY difference	Average cost of adding rHuEPO to transfusions: US$4,568 RBC transfusions alone: US$206	Base case ICER, adding rHuEPO to transfusions vs RBC transfusions alone: US$189,652 per QALY	Saving blood transfusions by adding rHuEPO increased quality-adjusted life expectancy by 8.4 days	Non-myeloid	'Any chemotherapy' and 'cisplatin-containing chemotherapy' scenario analysis
Borg 2008[9] [Sweden]	RBC transfusion alone	QALYs: EPO, 0.5687 RBCT, 0.53334	EPO: €3,750 RBCT: €2,881	ICER EPO vs RBCT: €24,700	None	Not specified	Not specified. Six (4-week) cycles
Cremieux 1999[12] [Based on US trials]	RBC transfusion	Changes in QoL (LASA scale) EPO: +8.30 mm Standard care: -1 mm	Over 16 weeks EPO: US$7,551 Standard care: US$1,416	Cost with epoetin of US$1 of standard care effectiveness: US$0.81	ICERs of US$110,769 to US$214,391, although values are unreliable	Multiple, including lung, breast, gynecological and gastrointestinal	Cisplatin- or non–cisplatin-based (16-week treatment)
Fagnoni 2006[13] [France]	No EPO	Only QALY difference reported	Without EPO: €34 With EPO: €1,649	EPO vs no EPO: €310,577/QALY	None	Breast	Six (3-week) cycles of standard adjuvant chemotherapy: anthracycline [adriamycin (50 mg/m^2) or epirubicin (100, 75 or 50 mg/m^2) and cyclophosphamide (500 mg/m^2) ± fluorouracil (500 mg/m^2)
Martin 2003[14] [UK]	Placebo	Total QALYs: epoetin alfa, 1.0375; placebo, 0.5570	Epoetin: £10,768 Placebo: £6,515	ICER cost epoetin vs placebo: £6,741/life year and £8,851/QALY	None	Stage IV breast	Three to six cycles, non-platinum-based
NICE 2014[15]; **Crathorne 2016**[16] [UK]	Best supportive care	Differences in QALYs reported. Total QALYs not given as QALYs were not reported for the no ESA arm. Total discounted, other ESAs vs no ESA: 0.0706 for all	No ESA: £912 Epoetin alfa Eprex: £2,414 Epoetin alfa Binocrit: £2,283 Epoetin beta: £3,384 Epoetin theta: £2,416 Epoetin zeta: £2,451 Darbepoetin alfa: £3,258	Base case results vs no ESA Epoetin alfa Eprex: £21,279 Epoetin alfa Binocrit: £19,429 Epoetin beta: £35,018 Epoetin theta: £21,309 Epoetin zeta: £21,804 Darbepoetin alfa: £33,233	Incremental NHB cost vs no ESA £20,000/QALY WTP threshold: epoetin alfa Eprex, -0.005; epoetin alfa Binocrit, 0.002; epoetin beta, -0.053; epoetin theta, -0.005; epoetin zeta, -0.006; darbepoetin alfa, -0.047 Incremental NHB cost vs no ESA £30,000/QALY WTP threshold: epoetin alfa Eprex, 0.021; epoetin alfa Binocrit, 0.025; epoetin beta, -0.012; epoetin theta, 0.020; epoetin zeta, 0.019; darbepoetin alfa: -0.008 At £20,000 per QALY WTP threshold, 48.1% put ESAs below threshold	Multiple	Platinum- and non-platinum-based
Roungrong 2008[17] [Thailand]	Blood transfusion	Differences in Hb levels (g/dl) reported in: rHuEPO arm: Hb <8, 0.31; Hb 8–9, 0.34; Hb 9–10, 0.34 Transfusion arm: Hb<8, 0.28; Hb 8–9, 0.30; Hb 9–10, 0.35	EPO: <8, ฿127,937; 8–9, ฿ 112,621; 9–10, ฿ 97,141 Transfusions: <8, ฿11,434; 8–9: ฿11,434; 9–10: ฿11,434	ICER, EPO vs transfusions: <8, ฿3,789,762; 8–9, ฿2,746,506; 9–10, dominant Ceiling threshold: ฿300,000 per QALY in Thailand	None	Not specified	Not specified. Six (4-week) cycles
Tonelli 2009[18]; **Klarenbach 2010**[19] [Canada]	No ESA	Not reported	Not reported	Base case. ESA, cost per QALY: Can$267,346; cost per life year: -$1,440,500 1-year time frame, ESA strategy dominated by no ESA (Can$100,500 per QALY)	None	Hematological (21%), solid (63%), and mixed (17%)	Not specified. Model cohort received chemotherapy (80%), radiotherapy (4%), and no chemotherapy (15%)
Wilson 2007[20] [UK]	Blood transfusion only	Not reported	Not reported	ICER EPO vs supportive care: £150,342	None	Not specified	Not specified. Six (4-week) cycles followed by no chemotherapy for thirty-three (4-week) cycles

*First- or second-line chemotherapy not specified in any of the studies

EPO: erythropoietin; ESA: erythropoiesis-stimulating agent; Hb: hemoglobin; ICER: incremental cost-effectiveness ratio; iNHB: incremental net health benefit; LASA: linear analog scale assessment; NHB: net health benefit; QALY: quality-adjusted life year; QoL: quality of life, RBCT: red blood cell transfusion; rHuEPO: recombinant human erythropoietin; WTP: willingness to pay.

- A fourth study stated that $0.81 spent on epoetin treatment yielded the same effectiveness as $1 spent on SoC, deducing that epoetin was 23% more cost-effective than SoC (**Table 1**)[12]
  - Incremental cost-effectiveness ratios (ICERs) were reported in this study, but the authors considered them invalid due to the broad range of cost per quality-adjusted life year (QALY) estimates in different, plausible scenarios, and the dependence of patients' initial disease state on the value assigned to a change in quality of life (QoL) measurements[12]
- In contrast, five studies presented unfavorable results for rHuEPO and concluded that ESAs were not cost-effective compared with SoC (**Table 1**)[11,13,17,18,20]
- Cancer treatment was reflected differently in the models assessed (**Table 1**)
  - Although the duration of chemotherapy was defined in most models, all but two models had heterogeneous populations, reflecting multiple cancer types
  - The studies with heterogeneous populations did not account for varying treatment patterns across cancer types, with three studies applying a fixed duration of chemotherapy to the model[9,17,20] and three others giving very little information on the cancer treatment[11,12,15]
- Limitations of the included studies included assumptions around hemoglobin normalization (hemoglobin levels returning to normal after completion of cancer treatment) and a lack of robust evidence for estimating survival benefit and HRQoL

CONCLUSIONS

- Evidence for the cost-effectiveness analyses of ESAs as SoC for the treatment of CIA is mixed, and therefore inconclusive
- Of the studies assessed, there were examples of models for short- and long-term economic evaluation of ESAs; long-term time horizons in the economic model are beneficial as it allows for modelling of long-term survival
- Among studies that were analyzed, there was extensive heterogeneity in trial design and patient populations, which led to difficulty in interpreting the economic model results
  - In addition, different country settings with the use of local costs made comparisons between studies difficult
- Future research should focus on investigating potential survival benefits of EPO and alternative approaches to estimating HRQoL and utility values for the economic models, such as patient preference-based QoL measures

Disclosures
CA is an employee of Astellas Pharma Inc.; AFA is an employee of Astellas Pharma Europe B.V.; AM is an employee of Astellas Pharma Europe Ltd.

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