Overview of Systematic Review and Economic Evaluation of Erythropoiesis-Stimulating Agents for Anemia of Cancer or of Chemotherapy
Until April 2006, the Canadian Agency for Drugs and Technologies in Health (CADTH) was known as the Canadian Coordinating Office for Health Technology Assessment (CCOHTA).


Production of this report is made possible by financial contributions from Health Canada and the governments of Alberta, British Columbia, Manitoba, New Brunswick, Newfoundland and Labrador, Northwest Territories, Nova Scotia, Nunavut, Ontario, Prince Edward Island, Saskatchewan, and Yukon. The Canadian Agency for Drugs and Technologies in Health takes sole responsibility for the final form and content of this report. The views expressed herein do not necessarily represent the views of Health Canada or any provincial or territorial government.

Reproduction of this document for non-commercial purposes is permitted provided appropriate credit is given to CADTH.

CADTH is funded by Canadian federal, provincial, and territorial governments.

Legal Deposit – 2009
National Library of Canada
ISSN: 1203-9012 (print)
ISSN: 1481-4501 (online)
O0468 – April 2009

PUBLICATIONS MAIL AGREEMENT NO. 40026386
RETURN UNDELIVERABLE CANADIAN ADDRESSES TO
CANADIAN AGENCY FOR DRUGS AND TECHNOLOGIES IN HEALTH
600-865 CARLING AVENUE
OTTAWA ON K1S 5S8
Canadian Agency for Drugs and Technologies in Health

Overview of Systematic Review and Economic Evaluation of Erythropoiesis-Stimulating Agents for Anemia of Cancer or of Chemotherapy

April 2009

We thank Lisa Hum for her assistance in creating this overview from a longer report authored by Tonelli et al.

1 Introduction

Of the more than 160,000 Canadians in whom cancer was diagnosed in 2008, approximately 30% will develop anemia. Anemia that is related to cancer (ARC) may be due to the cancer, a condition that occurs at the same time as the cancer (such as bleeding), or a complication of cancer treatment. Because anemia is associated with adverse clinical outcomes (for example, impaired quality of life [QoL], decreased survival), the treatment of anemia can improve the outcomes of people with cancer.

Erythropoiesis-stimulating agents (ESAs) are medications that can be used to manage anemia in people with cancer or other diseases. ESAs include epoetin alfa (Eprex, Janssen-Ortho Inc.), epoetin beta (NeoRecormon, Hoffman-La Roche Ltd.), and darbepoeitin (Aranesp, Amgen Canada Inc.). Epoetin alfa and darbepoeitin are available in Canada. Epoetin beta, which is similar to epoetin alfa, is widely used in Europe but unavailable in Canada. Continuous erythropoeitin receptor activator (CERA) is being studied and is unavailable in Canada. In this overview, “epoetin” refers to epoetin alfa or epoetin beta, and “ESA” refers to epoetins (alfa or beta) and darbepoeitin.

Epoetin and darbepoeitin, which elevate or maintain the level of red blood cells, are not intended for the treatment of severe anemia that requires immediate correction. Because of its longer half-life in plasma, darbepoeitin can be administered less often than epoetin. It is typically administered once every three weeks in patients with cancer. Epoetin and darbepoeitin are used for the treatment of anemia in patients with non-myeloid malignancies where anemia is due to the use of chemotherapy. Epoetin and darbepoeitin are also used for the treatment of anemia that is associated with chronic renal failure, and epoetin is indicated for the treatment of transfusion-dependent anemia that is related to therapy with zidovudine in patients who are infected with HIV, and the treatment of patients who are undergoing surgery to reduce allogenic blood transfusions.

Alternatives or complements to the use of ESAs include no treatment, iron therapy (for iron deficiency), and red blood cell transfusion. Clinical practice guidelines indicate when ESAs should be used by patients with cancer in preference to the use of blood transfusion and vice versa.4

The expected cost per week of ESA therapy for ARC is $350 to $450. The reimbursement policies for the use of ESAs vary across Canada. Given that ESAs are commonly used by Canadian patients with cancer, ESAs can be a cost driver. Because the risk of transmitting infectious illnesses through blood transfusion is thought to be less than it was, there is interest in evaluating the effectiveness and cost-effectiveness of ESAs. Studies suggest that in patients with cancer, the use of ESAs may be associated with an increased risk of adverse events such as the obstruction of blood vessels. There has been controversy about the adverse events that may occur after the use of ESAs by patients with chronic kidney disease. An assessment of the clinical- and cost-effectiveness of ESAs in ARC, and the potential for harm, would be useful to Canadian jurisdictions that are developing an evidence-based reimbursement policy.
2 Objectives

The objectives were to perform a systematic review of the clinical efficacy and harms of the use of ESAs and to conduct an economic evaluation and budget impact analysis that assess the use of ESAs by adult patients with ARC. The objectives were achieved by addressing four research questions:

• What is the clinical-effectiveness (benefits and harms) of using ESAs for the treatment of ARC, including the treatment of chemotherapy-induced anemia?
• What is the cost-effectiveness of using ESAs in Canada for the treatment of ARC, including the treatment of chemotherapy-induced anemia?
• Are there differences in the clinical- and cost-effectiveness of ESAs based on the type of cancer?
• Are there specific groups of patients for whom red blood cell transfusions are not options for the treatment of ARC and for whom the benefits of ESA therapy differ from the general population?

3 Clinical Review

Methods

Published literature was obtained by cross-searching MEDLINE, EMBASE, and all EBM Reviews. Grey literature was obtained by searching cancer and trial registries and through hand searches of reference lists of reviews. The Canadian manufacturers of ESAs and the authors of included studies were contacted. Included studies were parallel randomized controlled trials (RCTs) with 30 participants or more in each treatment group; enrolled adults with anemia (18 years of age or older) and with cancer; and evaluated alfa and beta epoetin, darbepoetin, or CERA compared with a different agent, no ESAs (for example, placebo), or a different method of delivery (dose, schedule, route of administration, fixed or weighted dose). Outcomes were all-cause mortality, cardiac events (myocardial infarction, stroke, heart failure, or revascularization), hospitalization, QoL, hypertension, red cell transfusions, and adverse events.

Two reviewers independently screened each citation or abstract, and applied the selection criteria to the full text of potentially relevant articles. One reviewer extracted data, and two reviewers checked for accuracy. The trial characteristics, study participants, illness severity, therapeutic regimens, control regimens and co-interventions, and outcomes were recorded. Data were gathered on the outcomes of mortality (all-cause), cardiovascular events, hospitalization, QoL, red cell transfusions, hypertension, and adverse events. Adverse events were classified as serious if they were defined as such in the trials or if an adverse event of unspecified severity led to the patient’s withdrawal from therapy or the study. Attention was focused on the incidence of seizures and thrombotic events. Only QoL measures that were used in more than one study were considered in each comparison. The study quality was independently assessed by two reviewers using a condensed version of the Chalmers Index. The study quality and funding sources were recorded. Reviewers’ differences about trial selection or study quality assessment were resolved with a third party through consensus.
The results were pooled for trials that compared ESA with no ESA (placebo or no treatment), early intervention with ESAs with late intervention, and darbepoetin with epoetin. Relative risk (RR) and weighted mean difference were used to summarize dichotomous and continuous results respectively. The results were combined using a random effects model, and statistical heterogeneity was quantified using $I^2$. Regression methods, sensitivity analyses, and analyses of subgroups were used to examine the relationship between therapy and clinical outcome.

**Results**

In the literature search, 1,948 citations were identified. After screening, 76 primary trials met the selection criteria.

a) **Erythropoiesis-Stimulating Agents versus No Erythropoiesis-Stimulating Agents**

Of 52 trials (12,006 participants) of poor to moderate quality, 42 trials (7,356 participants) compared epoetin alfa or epoetin beta with no ESA, and 10 trials (4,650 participants) compared darbepoetin alfa with no ESA. The median number of participants was 153, and the range was 60 to 989 participants. Based on 28 trials (6,525 participants), the all-cause mortality during treatment differed between groups, favouring no ESA. There were no differences between groups in the risk of cardiovascular events (3,281 participants) or the incidence of hypertension (3,792 participants). Four trials (895 participants) on the duration of hospitalization could not be combined. Among the four trials, three studies reported no differences between groups, and one study found a shorter duration with ESAs. The use of ESAs was associated with clinically relevant improvement in QoL (1,326 participants) as indicated on the Linear Analog Scale Assessment, Functional Assessment of Cancer Therapy-Fatigue, and Functional Assessment of Cancer Therapy-Anemia (FACT-Anemia) subscale scores. Compared with no ESA, treatment with ESAs prevented transfusions (5,321 participants), but led to an increased risk of thrombotic events (3,420 participants) and serious adverse events (5,891 participants). The pooled RR (247 participants in two trials) of tumour response that was associated with the use of ESAs was not different from that of the control. Restricting the analyses to studies that used ESAs according to the American Society for Clinical Oncology (ASCO) criteria resulted in a smaller evidence base (289 participants). There was no evidence that the risks or benefits of ESA treatment in this group differed from those in the overall population of patients who were treated with ESAs for ARC.

b) **Early versus Late Erythropoiesis-Stimulating Agents**

The two trials (470 participants) of early versus late ESA were of poor quality. Both trials reported all-cause mortality at one month and 18 months follow-up. Fewer deaths were reported with early ESA intervention. The results were not statistically significant. The pooled RR for cardiovascular events was also not statistically significant. The evidence from one trial (232 participants) indicated that early ESA intervention improved QoL. The reported change score weighted mean differences were statistically significant for the General, Fatigue, and Anemia subscores of the FACT-Anemia scale and the Total FACT-Anemia score. This trial reported a change in overall QoL on the Linear Analog Scale Assessment scale, although this did not exceed a clinically important difference. Based on the two trials, the risk of receiving transfusions was reduced by 33% with early ESA intervention compared with later intervention. In one trial (269 participants), the tumour response was not statistically significantly different between early versus later ESA intervention. Two cases and one case of hypertension were
reported with early and later ESA intervention respectively. The direction of effect for serious adverse events was inconsistent between the trials, and the results were not pooled. The pooled risk of thrombotic events was greater among patients who received early compared with later intervention.

c) Darbepoetin versus Epoetin

The six trials\textsuperscript{16-21} of darbepoetin versus epoetin were of poor quality. No difference was observed between the two agents in the risk of all-cause mortality in two trials (1,567 participants) or in the risk of cardiovascular events in one trial (352 participants). There was also no statistically significant difference in QoL between agents, as indicated by the scores on the Anemia subscale (729 participants) and the Fatigue subscale (830 participants). The risk of transfusion was not statistically different between groups in one trial (141 participants) that reported the number of participants who received transfusions during treatment and in three trials (1,676 participants) that reported the number of transfusions. One trial reported fewer transfusions with the use of darbepoetin; the other two trials reported the opposite. Although more serious adverse events were observed with the use of epoetin alfa than with darbepoetin in one trial (141 participants), the RR was not statistically significant. The pooled RR from three trials (1,702 participants) indicated less risk of thrombotic events with darbepoetin, but this was not statistically significant.

d) Supplemental Issues

Sixteen trials\textsuperscript{16,17,22-35} of poor to moderate quality included supplemental issues. Because different doses were compared for CERA, epoetin, and darbepoetin, the data were not pooled. None of the individual RRs was statistically significant.

Comparisons by dosing schedules were based on poor-quality studies, and none of the results was statistically significant. One trial of poor quality reported no difference between the routes of administration in the risk of death or in the frequency of blood transfusions. In three poor-quality trials, the risk of death was not different between fixed and weight-based doses. One or more of these three trials found no difference in the number of transfusions, the number of seizures, and the incidence of cardiovascular events, hypertension, and thrombotic events.

4 Economic Review

Methods

In addition to the search results from the clinical review, citations from economic searches conducted in MEDLINE, EMBASE, EconLit, and the NHS Economic Evaluation database were screened. Studies were included if they evaluated the incremental impact of an ESA against a comparator group on costs and health outcomes and if the comparator group included a placebo, no ESA, different ESA, or same ESA but varying hemoglobin target, dose, or schedule. The comparisons of different ESAs or comparisons of alternative route or schedule of administration of ESAs to achieve a similar hemoglobin target were included in a cost-minimization analysis if they were based on RCT data on effectiveness. Studies were required to examine a cohort of adult patients with malignancy and anemia. Reviewers applied the selection criteria and
extracted data including author, title, intervention, comparators, study population, study design, time horizon, perspective, data sources for effects, data sources for costs, health-related QoL, currency, year, base-case incremental cost-effectiveness ratio results or incremental net benefit, sensitivity analysis, and conclusions. The study quality was independently assessed by two reviewers using a checklist. As planned, a qualitative synthesis of included studies was conducted.

**Results**

Of 1,134 citations that were identified from the combined searches, 11 studies met the selection criteria. The study characteristics and study quality assessments appear in the full report. The economic review focused on the limitations and relevance of studies, costs, QoL, and the applicability of the findings to a contemporary Canadian setting. The details appear in the full report.

The included studies consistently reported large incremental costs when ESA strategies were compared with standard care. These were largely driven by the acquisition costs of the ESA. This result was not altered by a range of costs for blood transfusion or by most short- or long-term adverse events that were related to the use of ESAs or blood transfusion. The cost and cost-effectiveness analyses (in which hemoglobin was used as a measure of effectiveness) indicated an increased cost with the use of ESAs but did not provide insight into the relative value of the health benefits that were achieved. Among studies that converted health outcomes into a common metric, such as QALYs or cost (cost-utility and cost-benefit), most of the base-case analyses indicated that the treatment of ARC with ESAs exceeded a reasonable value for the health resources that were consumed. Of the 10 studies that evaluated ESAs compared with standard care, seven suggested that the use of ESAs in patients with cancer who were receiving chemotherapy does not represent good value for money. The incremental cost-utility ratio (ICUR) was sensitive to the assumption of a benefit in mortality with ESAs — although the evidence for a benefit was lacking.

A limitation of the studies was the absence of RCTs that used preference-based utility scores as an outcome. The methods of assigning a utility score using a transformation of disease-specific measures or using observational data (where utility is assigned based on achieved hemoglobin) may lead to biases that favour ESA treatment. Despite this, many studies that used this approach did not report an attractive ICUR based on stated thresholds or based on commonly cited standards. These findings are reinforced by analyses that quantified health outcomes using a willingness-to-pay approach.

5 **Economic Evaluation**

**Methods**

The cost-utility and cost-effectiveness analyses were conducted to determine the cost-effectiveness of using ESAs to treat patients with cancer and anemia, compared with a strategy of managing anemia without ESAs (including supportive red blood cell transfusion). The population included adults who were enrolled in clinical trials of ESAs for the management of
ARC (average age of 62 years, initial hemoglobin of 10.4 g/dL, 23% with hematological malignancy, 80% being treated with chemotherapy). The base-case analysis compared no ESA use versus ESA use, allowing for blood transfusions in both arms. Epoetin was considered in the base case, and darbepoetin was considered in the second analysis. An economic decision model was created for the base case, and in the secondary analysis a Markov process was added to account for outcomes that occur over an additional year. The outputs of the model were QALYs, life-years gained, health care costs, and the cost per QALY gained. The base-case analyses were performed using Markov cohort analysis, and Monte Carlo simulation was used for the probabilistic sensitivity analysis. All costs were reported in Canadian dollars. The target audience included provincial health ministries and regional cancer programs that provide care to cancer patients with anemia. The primary perspective was that of the Canadian publicly funded health care system. In the primary analysis, a time horizon that was consistent with the duration of outcome ascertainment was used in the included trials (15 weeks). An additional year was considered in the secondary analysis. The information sources for outcomes (mortality, red blood cell transfusion, adverse outcomes, QoL), resource use and costs, assumptions, and potential limitations appear in the full report.13 The sensitivity and scenario analyses were conducted to explore the variability and uncertainties in the model.

Results

In the base-case analysis, when compared with no ESA and supportive transfusion, treatment with epoetin resulted in incremental costs of $8,643, incremental benefits of 0.03 QALYs over 15 weeks, and an ICUR of $267,346. When a one-year time frame was considered, the ESA strategy was dominated by no ESA, with incremental costs of $8,643 and lower QALYs (~0.086). Similar results were obtained for the costs of darbepoetin. The base-case analysis using cost per life-year gained resulted in incremental costs of $8,643 and −0.006 life-years for the no ESA arm (the ESA strategy dominated by no ESA).

In the sensitivity analyses, the variation in the costs of blood transfusion, weekly dose and duration of epoetin, and cost per unit had no qualitative impact on the results. The use of an alternative method of incorporating the reduction of transfusions in the ESA arm (using information on the baseline risk of transfusion, RR of transfusion, and the number of units that were transfused) resulted in an ICUR of $272,496. These results were robust for the three variables. In the assessment of long-term (one-year) mortality, the ESA strategy was dominated (except when the lower 95% confidence interval for the RR of mortality at 15 weeks and for the one-year mortality were used), leading to an ICUR of $100,984. Alternative estimates of QoL benefits and methods of incorporating reduced transfusion did not lead to reductions in the ICUR, although some resulted in ICURs up to $1.1 million/QALY. The ICUR was $125,668 in a scenario where assumptions about QoL all favoured the ESA strategy. The use of the assumption that there is no increased risk of mortality with ESAs did not alter the results.

In scenario analyses that simulated the use of ESAs in accordance with current practice guidelines, ESA therapy was dominated in three analyses, the ICUR was greater than $100,000/QALY in four analyses, and the ICUR exceeded $70,000/QALY in all analyses. There was uncertainty for many of the model parameters that were used. When ESAs were assumed to lead to a benefit in mortality among patients who met the ASCO criteria, the cost per QALY was $139,691. If the effect of ESAs on mortality in patients who met the ASCO criteria was assumed
to be consistent with that in the base case, then ESA was dominated by the no-ESA strategy. These findings suggest that ESA therapy for patients with cancer is unlikely to be economically attractive when commonly accepted standards are used.49,50

6 Limitations

The clinical review’s results and strength of conclusions were limited by poor to moderate trial quality, which may have reduced internal validity. Because most trials had short on-treatment follow-up, a sensitivity analysis to pool post-treatment mortality data was performed. This excluded more than half of the studies and included follow-up time after participants had stopped the therapy that they were randomized to receive. A meta-regression was performed to examine whether the effect of ESAs on mortality and other clinical outcomes differed in certain groups of patients. The effect of ESAs on mortality seemed to be homogeneous, but a meta-regression has limitations.51 Because of limited evidence and the limitations of meta-regression, the possibility that the risk-to-benefit ratio of certain strategies for ESA use cannot be discounted. Available data are insufficient to confirm or refute these hypotheses. Because few data compare the clinical effects of individual ESAs (for example, darbepoetin versus epoetin or subcutaneous versus intravenous administration), it is speculative that one agent or route of administration might be more beneficial than the other. The identification of populations that are especially likely to benefit from ESA therapy was tested using meta-regression wherever possible. All these analyses were non-significant. We were unable to locate studies that specifically informed this issue.

As in most economic evaluations, the models and results were limited by the evidence and the requirement to model all relevant clinical and economic consequences. A lack of strong evidence from RCT data on the incremental changes in utility-based QoL was addressed by incorporating assumptions that favoured the ESA arm. This model, however, did not incorporate other considerations that may affect QoL, including cyclical hemoglobin values, aversion to intravenous administration, and receipt of human blood products. The economic analysis considered the costs that were attributable to anemia and its treatment, but it excluded the health care costs that were attributable to other aspects of cancer and its treatment. The increased risks of serious adverse events and thrombotic events with ESA use were not incorporated into the model because of a lack of data on their impact on costs and QoL. Thus, the health benefits may be lower and costs higher for the ESA strategy than those that were presented here. The analyses on the cost-effectiveness of ESAs in groups of patients who met ASCO criteria were limited by the availability of few studies, the inclusion of studies that used ESAs in a way that was not identical to that in the ASCO criteria, and the incomplete reporting of parameters. Although uncertainty about the incremental costs and benefits of ESA therapy in this group remains, there was no evidence to suggest that ESAs are more economically attractive in this group than in any other.
7 Health System Implications

For patients with cancer and anemia who are undergoing treatment, the estimated cost of managing anemia with ESAs using a threshold hemoglobin of less than 10 g/dL is C$43 million to C$73 million annually in Canada. Because of limitations in the data, it was only possible to estimate the cost based on initial hemoglobin or reimbursement in Québec. The costs are likely to be lower in provinces with more restrictive criteria. If the criteria for reimbursement lead to the funding of ESAs for patients with cancer who are not undergoing active treatment, the total costs may be higher. Changes to the Health Canada labels for epoetin and darbepoetin and the more restrictive criteria that are recommended in newer practice guidelines will likely reduce future ESA use.

An estimated 7,000 to 14,000 Canadian patients receive treatment with ESAs for cancer each year. Assuming that life expectancy and underlying diagnoses among Canadian patients with cancer is similar to those in the studies that are included in this review, the use of ESAs may result in 137 to 275 deaths and 333 to 667 serious adverse events per year.

8 Conclusion

The use of ESAs in patients with cancer led to clinical improvements in QoL and decreased the risk of red cell transfusions. The use of ESAs, however, led to an increased risk of all-cause mortality, an increase in the risk of serious adverse events, and cost-utility ratios that exceeded the commonly accepted standards for economic attractiveness. There was no evidence that the risks or benefits of ESA therapy differed among patients who did or did not meet the revised criteria for its use in patients with cancer. These findings raise potential safety concerns about the use of ESAs to manage anemia in patients with cancer and suggest that using ESAs to manage ARC may not represent good value for money. The re-evaluation of existing practice guidelines and further review by payers and regulatory authorities may be advisable.

9 References