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ORIGINAL ARTICLE

The cost-effectiveness of treatment with erythropoietin compared to red blood cell transfusions for patients with chemotherapy induced anaemia: A Markov model

SIXTEN BORG[1], ANNA H. GLENNGÅRD[1], ANDERS ÖSTERBORG[2] & ULF PERSSON[1]

[1]*The Swedish Institute for Health Economics (IHE), Lund, Sweden and* [2]*Departments of Hematology and Oncology, Karolinska University Hospital, Stockholm*

Abstract

Background. Anaemia is a common complication of chemotherapy. As anaemia can lead to e.g. fatigue, depression, social isolation and chest pain it diminishes physical capacity and quality of life. It is generally accepted that symptomatic anaemia should be corrected. Treatment options include red blood cell transfusion (RBCT), erythropoietin (EPO) administration or a combination of both. *Objective.* The objective of this study was to carry out a cost-effectiveness analysis of treatment with EPO (epoetin alfa), compared to treatment with RBCT for patients with chemotherapy-induced anaemia in Sweden from a health care perspective. *Method.* A model was developed for estimating incremental costs and QALY gains associated with EPO treatment compared to treatment with RBCTs, based on a model commissioned by the UK National Institute for Health and Clinical Excellence and adjusted to reflect Swedish treatment practice. Data regarding patient characteristics, response rates, and RBCT was derived from a Swedish observational study of EPO treatment in cancer patients with chemotherapy related anaemia. Swedish guidelines and unit costs were used throughout the study. A systematic review of EPO for treatment of anaemia associated with cancer was used to estimate QALY gains associated with changes in Hb-concentrations in our model. *Results.* The model's results validate well to real world data from three major hospitals in Sweden. The cost per QALY gained from administration of EPO was estimated at EUR 24 700 in the base case analysis. Practicing an EPO treatment target Hb-level of 12 g/dl yields a cost per QALY about 40% lower than practicing a Hb-target level of 13 g/dl, which is in agreement with updated recommendations of using a 12 g/dl target. *Conclusion.* The estimated cost per QALY falls well within the range acceptable in Sweden when practicing a Hb-target level of 12 g/dl. The incremental cost of elevating Hb-levels above 13 g/dl is very high in relation to the incremental QALY gain achieved.

Anaemia, i.e. deficiency of red blood cells (RBC) is a common complication of chemotherapy [1]. In the European Cancer Anaemia Survey (ECAS), including 15 000 patients from 24 countries followed for 6 months, 68% of the patients had anaemia at some point. The prevalence of anaemia varied among types of cancer and disease status, e.g. among patients with gynaecological cancer 81% were anaemic at least once during the study period whereas the corresponding figure for patients with head and neck cancer and urogenital cancer was slightly above 50% [2]. In other studies, the prevalence of mild and moderate anaemia is reported to be between 32 and 100% in patients with haematological cancer and between 5 and 85% in patients with solid tumours [3,4].

As anaemia can lead to different symptoms, such as fatigue, depression, social isolation, respiratory distress and chest pain it diminishes physical capacity and quality of life. It is generally accepted that symptomatic anaemia should be corrected [5]. Anaemia treatment options include red blood cell transfusion (RBCT), erythropoietin (EPO) administration or a combination of both [1,6]. Currently, three forms of EPO are available on the European market: epoetin alfa, epoetin beta and darbepoetin alfa.

The costs and effects of EPO treatment in different patient groups have been widely discussed since the early 1990s [5,7]. In a study by Remák et al. [8], the change in cost-effectiveness of epoetin alfa treatment versus RBCTs for patients with renal

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Correspondence: Sixten Borg' The Swedish Institute for Health Economics (IHE), Box 2127, SE-220 02 Lund, Sweden

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failure in the UK between the years 1990 and 2000 was analysed. They found that the cost-effectiveness ratio had declined over the period and that by year 2000 it was within the range generally considered acceptable by the UK National Institute for Health and Clinical Excellence (NICE) [9]. The reduction was explained primarily by decreased dosage and price of EPO.

There is very limited information available about the cost-effectiveness of EPO treatment for cancer related anaemia. In most European countries, only a small proportion of all eligible cancer patients are treated with EPO. This has been further underlined by the ongoing safety discussion regarding epoetin usage in patients with cancer. The objective of this study was to carry out a cost-effectiveness analysis of treatment with EPO (epoetin alfa), compared to treatment with RBCT for patients with chemotherapy-induced anaemia in Sweden from a health care perspective.

Methods and data

A model was developed for estimating incremental costs associated with EPO treatment compared to treatment with RBCT alone. The model was developed and analysed using the R software version 2.4.0 [10]. Treatment strategies where patients are given EPO and complementary RBCT were compared to different strategies where patients are treated with RBCT alone. The model was based on a model commissioned by NICE [11], henceforth denoted the NICE model, and adjusted to reflect Swedish treatment practice. Data informing the model's parameters were taken from the NICE model, except data regarding patient characteristics and response rates associated with EPO and RBCT treatment which was obtained from a Swedish observational study [12]. The observational study is a retrospective chart review of 59 patients with cancer who developed chemotherapy-related anaemia and received treatment with an erythropoiesis-stimulating agent (29 patients on epoetin alfa and 30 patients on darbepoetin alfa). The study was performed at three Swedish hospitals to evaluate the utilisation, outcomes, and costs of using epoetin alfa or darbepoetin alfa. To our knowledge, this is the only applicable study of Swedish patients with chemo-therapy induced anaemia available.

Model description

Our model is a Markov model with time-dependent state transition probabilities. The states are defined by Hb-level intervals (<8 g/dl, 8–9 g/dl, 9–10 g/dl, 10–11 g/dl, 11–12 g/dl, 12–13 g/dl, and >13 g/dl) and by presence or absence of EPO treatment. The state space is further defined by the presence or absence of RBCT and response to EPO treatment. There is also a state for death. This structure was taken from the NICE model since it included the major factors influencing the problem at hand. Our only adjustment of this structure was that to reflect Swedish treatment guidelines for EPO (Figure 1). Our resulting model structure is shown in Figure 2. There are two treatment arms in the model; one with EPO treatment (complemented with RBCT when the Hb-levels falls below 10 g/dl) and one with RBCT treatment alone. Each cycle in the model lasts for 4 weeks. The expected health status, resource use and treatment costs are estimated for each cycle. A one-year time frame is used in the analysis.

In the EPO treatment arm, patients receive an initial EPO dose of 150 IU EPO/kg body weight, three times a week if the Hb-level is below 10 g/dl, i.e. in the interval 9–10 g/dl. The interval midpoint (9.5 g/dl) reflects Swedish treatment guidelines [13]. There is a fixed monthly response rate associated with EPO treatment of 55%, estimated from Persson

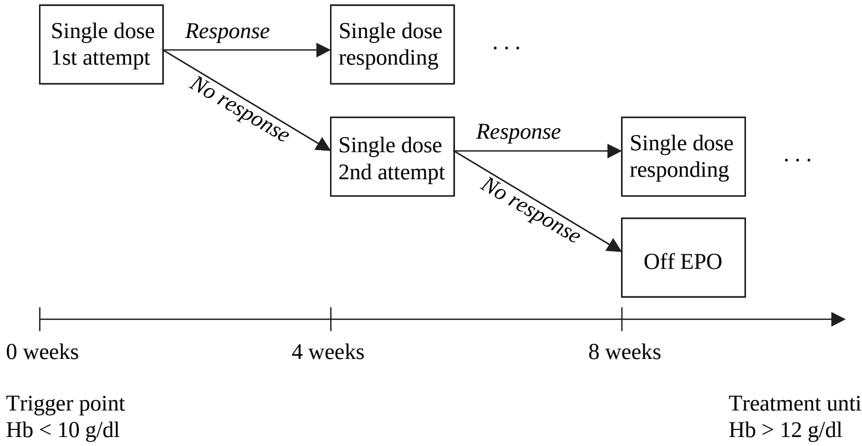

Figure 1. Swedish treatment guidelines for EPO, adapted to the model.

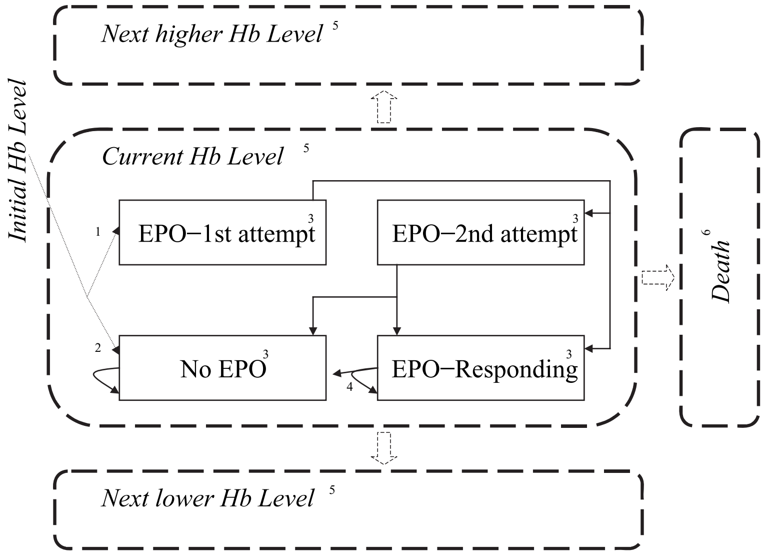

Figure 2. Model structure. At the patient's initial Hb level, EPO treatment is initiated during two attempts, EPO-1st attempt and EPO-2nd attempt, respectively. If the patient responds (EPO-Responding), treatment continues until the target Hb level is reached. Otherwise treatment is stopped (No EPO). The Hb level is increased by EPO response, RBCT and normalization, and decreased by chemo-therapy. At all times, there is a risk of death.

Notes:

1. Starting point for the EPO arms.
2. Starting point for the RBCT arms.
3. Each of these states are subdivided into RBCT and No RBCT, respectively, according to the current Hb level and trigger level for RBCT. If Hb $<$ trigger level, the patient visits EPO-1 & RBCT, EPO-2 & RBCT, EPO-Responding & RBCT or No EPO & RBCT, depending on EPO treatment status. Otherwise the patient visits EPO-1 & No RBCT, EPO-2 & No RBCT, EPO-Responding & No RBCT or No EPO & No RBCT, respectively.
4. The patient remains in the EPO-Responding state until the Hb level reaches the target level for EPO, in which case the patient moves to No EPO.
5. The Hb levels are <8, 8–9, 9–10, …, 12–13, >13 g/dl. Within each Hb level, there is a group of states representing current EPO treatment status, and RBCT status in patients with that Hb level as illustrated for Current Hb Level.
6. The Death state is accessible from all other states.

et al. [12], whereby the Hb-level rises with 2 g/dl per treatment cycle. If the patient does not respond to EPO treatment during the first treatment cycle, the dose is maintained at the initial level during the second cycle and in case the patient still does not respond during the second cycle, EPO treatment is terminated. Once the patient has responded, response is assumed to continue [14], and EPO treatment is maintained until the Hb-level has reached a target Hb-level. Costs and effects associated with two different target levels are modelled, i.e. one base-case scenario with a level of 12 g/dl (EPO_{LOW}), reflecting the recently updated Swedish treatment guidelines [13] and one scenario with a Hb-level of 13 g/dl (EPO_{HIGH}) reflecting treatment practise in Sweden before 2007 [12]. The base-case EPO treatment algorithm is shown in Figure 1.

The EPO treatment strategy is compared to different strategies where patients are treated with RBCT. Each RBCT corresponds to two units filtered red blood cells. The first RBCT incurs a response of 1 g/dl rise in Hb-level. If a RBCT occurs also in the next cycle, the Hb-level remains at the level achieved by the first RBCT, together with any other simultaneous effects on Hb-level. In the base-case scenario, treatment with RBCT is initiated when the patients Hb-level falls below 10 g/dl (RBCT_{10}), which should reflect Swedish treatment practice. In sensitivity analyses, the EPO treatment strategy was compared to RBCT treatment where the trigger point Hb-level was set at 9 g/dl (RBCT_9), and 11 g/dl (RBCT_{11}). In these analyses, the default RBCT trigger point of 10 g/dl was replaced by new values, i.e. 9, and 11. The RBCT_9 strategy should reflect European treatment practice and the RBCT_{11} strategy should reflect a more aggressive RBCT treatment scenario where it is attempted to reach high Hb-levels without EPO administration.

Chemotherapy lasts for six treatment cycles in the model. The duration is fixed, and we assume no treatment withdrawals. In the absence of anemia treatment, of if no response to EPO or RBCT treatment, the Hb-level will fall by 1 g/dl per treatment cycle. After completed chemotherapy, the Hb-level is assumed to undergo normalisation, whereby the Hb-level will rise by 1 g/dl per treatment cycle until the Hb-level reaches 13 g/dl. In a sensitivity analysis, a rise of 2 g/dl per cycle was analysed.

The change in health status is measured as changes in Hb-concentrations, associated with changes in quality of life. Measuring health-state utility is usually based on a definition of utility as individuals' relative preferences between different health states. Normally a scale between 0 and 1 is used, where 0 represents death or the worst-case scenario and 1 represent perfect health. Quality Adjusted Life Years (QALYs) is survival weighted by utility, and this is a commonly accepted measure of health benefit from a certain intervention. During each cycle in the model, the Hb level (mean Hb before and after the chemotherapy, EPO and RBCT increments/decrements) is used to determine the utility weight.

Data

Data regarding patient characteristics, response rates, and RBCT is derived from a Swedish observational study of EPO treatment in cancer patients with chemotherapy related anaemia, where response in terms of changes in Hb level was measured [12]. The observed survival was used in both arms of the model, i.e. it was assumed that the survival effect associated with EPO treatment is neutral [15]. Swedish guidelines and unit costs are used throughout the study. Costs are expressed in Euro (EUR) and in Swedish kronor (SEK). All costs were valued at 2007 prices. The exchange rate 9.1994 SEK/EUR is used. Updated Swedish recommendations regarding EPO administration [13], and Persson et al. [12] and Pharmaceutical Specialities in Sweden, FASS [16], were used to inform the model's treatment practice.

The EPO response rate was estimated based on Persson et al. [12], using a model calibration procedure in which the model parameters for RBCT, EPO treatment, and initial Hb, were tuned to reflect the conditions in the study, and the response rate that provided the best validation of Hb outcome was taken as our estimate. Using the Hb change from baseline and the proportion of patients reaching a Hb level above 12 g/dl as target for the calibration yielded an estimated response rate of 55% per treatment cycle. In Persson et al. [12], the EPO dose was doubled after four weeks in case of no response. In the present study, the model follows current treatment recommendations, whereby treatment with single dose is continued in case of no response to EPO treatment (Figure 1). Thus, the response rate has been adjusted. There is lack of robust evidence of improved response by increasing the dose in non-responders [5], although studies indicate that the response rate may be increased by up to 12% in 8 weeks [17], and up to 17% in 12 weeks [18], by doubling the dose. We have assumed that by 8 weeks (two treatment cycles), the EPO response rate is 70% to EPO single dose, and when doubling the dose for non-responders after 4 weeks (one treatment cycle) the response rate will be 80%. This translates to monthly fixed response rates of 45% and 55%, respectively.

A health care perspective was used in the cost analysis. Unit costs for pharmaceuticals were derived from Pharmaceutical Specialities in Sweden, FASS [16] and hospital unit costs were derived from the price list of the Southern Health Care Region for 2007 [19]. The cost of EPO is based on the cost of Eprex; EUR 1 329 (SEK12 222; 0.097*150*70*3*4) per four-week cycle, assuming normal dose and patient body weight of 70 kg [16]. The cost of double dose is twice as high. It is assumed that the patients make one initial visit with a nurse at the oncology department and thereafter administers the drug subcutaneously at home. The cost of visiting a nurse at the oncology department used in the study is EUR 40 (SEK 372) [19]. The cost of one unit transfused filtered RBC used is EUR 187 (SEK 1 717), including compatibility testing and cross match [19]. It is assumed that each RBCT incurs a visit at the oncology department at the rate of EUR 400.

Data concerning the relation between Hb-concentrations and quality of life was taken from the NICE model, where the results of a systematic review of EPO for treatment of anaemia associated with cancer were used to estimate QALYs associated with changes in Hb-concentrations [14] (see Table I). The utility levels in the table are measured using the Time-Trade-Off (TTO) method.

The initial Hb levels in the patient population in the model is presented in Table I. This distribution was used in both treatment arms of the model, in all analyses except the sensitivity analyses with regards to initial Hb level.

Table I. Utility level by Hb-concentration and distribution of Hb level in the patient population at the start of the model evaluation.

	Hb-level g/dl	Utility level	% of the patients
Severe anaemia	<8	0.466	3%
Moderate anaemia	8–9	0.563	21%
	9–10	0.631	38%
Mild anaemia	10–11	0.692	28%
	11–12	0.749	10%
	12–13	0.789	0%
No anaemia	>13	0.810	0%

Source: Wilson et al. [14].

Results

EPO versus RBCT treatment according to Swedish practice (base case)

Administration of EPO according to current recommendations (EPO_{LOW}) versus RBCT treatment alone with a trigger of 10 g/dl ($RBCT_{10}$), resulted in an estimated cost per QALY of EUR 24 700 (SEK 227 000) (Table II). The increase in total costs was estimated at EUR 870 (SEK 8 000). About two thirds of the EPO cost is offset by reductions in the cost of RBCT. Administration of EPO compared to treatment with RBCT alone leads to a more effective correction of the Hb-level, whereby it rises faster and remains at a higher level, resulting in a gain of 0.0353 QALYs.

The cost per QALY differs only slightly depending on the patients Hb-level at the start of treatment. The range was estimated at between 23 150 and 29 130 EUR/QALY (213 000 and 268 000 SEK/QALY) for initial Hb-levels in the interval less than 8 g/dl to 9–10 g/dl. In both arms, lower initial Hb-levels cause the total cost to increase and the QALYs to decrease. In the EPO arm, the ranges are 4 435 to 6 174 EUR, and 0.59 to 0.57 QALYs, and in the RBCT arm, the ranges are 3 022 to 3 935 EUR and 0.53 to 0.49 QALYs, for initial Hb levels of 9–10, 8–9, and below 8 g/dl. Since EPO treatment will not be initiated if the initial Hb-level is above 10 g/dl, higher initial Hb levels have not been analysed.

Costs and effects associated with different strategies

In Figure 3, the costs and effects associated with different EPO and RBCT treatment strategies are shown. The RBCT strategies differ by their trigger point for RBCT (9, 10, and 11 g/dl). Between these strategies, the marginal effect on QALY decreases for each step, while the increase in cost remains fairly constant.

Using a higher target level for EPO treatment, 13 g/dl (EPO_{HIGH}), causes EPO costs to increase to 24 500 SEK. The cost per QALY versus $RBCT_{10}$ is 39 800 EUR/QALY (366 000 SEK/QALY), because of a slightly higher QALY gain of 0.0371. The cost per QALY of EPO_{HIGH} versus EPO_{LOW}, however, is estimated at 336 500 EUR/QALY (3 096 000 SEK/QALY), resulting from an incremental cost of 609 EUR and hardly any QALY gain, 0.0018 QALYs.

When altering the trigger level for RBCT to between 9 and 11 g/dl, the cost per QALY for EPO administration versus treatment with RBCT alone ranges between 19 500 and 31 850 EUR/QALY (179 000 and 293 000 SEK/QALY). Both the incremental costs and the QALY gains of EPO treatment versus RBCT treatment become larger as the RBCT trigger level becomes lower.

The proportion of patients with anaemia is lower in the EPO treatment groups at 3 and 6 months. By 9 months, $RBCT_{11}$ is slightly less anaemic. After 6 months of treatment, more than 75% of the patients in the RBCT treatment groups are anemic. In the $RBCT_9$ and $RBCT_{10}$ more than half of the anaemic patients have at least moderate anaemia. The baseline values are identical in all treatment groups. Chemotherapy is assumed to stop after 6 months whereby the patients Hb-concentrations undergo normalisation. This is seen to some extent by 9 months. By 12 months no patients are anaemic with any of the treatment strategies.

Costs and effects associated with different Hb normalisation rates

We have modelled Hb normalisation after completion of the chemotherapy with a rate of a 1 g/dl rise per cycle. This results in a mean time of 10 weeks from the end of chemotherapy until the mean Hb-level is above 12 g/dl in the EPO arm in the base-case scenario. In the RBCT arm, the corresponding time is 14 weeks. With a normalisation rate 2 g/dl rise per cycle, these values become 4 and 7 weeks, respectively. The cost of RBCT becomes slightly lower in both arms of the model, EUR 11 less in the EPO arm and EUR 22 less in the RBCT arm. The EPO cost does not change, since most of the effect of quicker normalisation occurs above the target level for EPO. The resulting incremental cost-effectiveness ratio is 29 500 EUR/QALY (271 000 SEK/QALY).

Table II. Costs (EUR), QALYS and Incremental cost per QALY (ICER, EUR/QALY) of EPO_{LOW} compared to $RBCT_{10}$ treatment, base case.

Strategy	EPO cost	RBCT cost	Total cost	QALY	ICER
EPO_{LOW}	2 054	1 696^A	3 750	0.5687	
$RBCT_{10}$	0	2 881^B	2 881	0.5334	
Difference	+2 054	−1 185	+870	+0.0353	24 700

Notes: ^{A}Corresponding to 4.1 RBCTs. ^{B}Corresponding to 7.0 RBCTs.

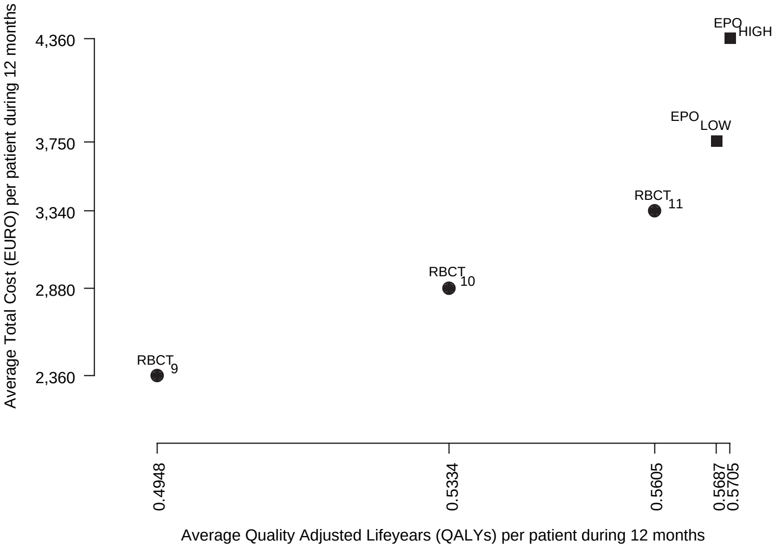

Figure 3. Costs and effects of different treatment strategies for treatment of chemotherapy related anaemia, SEK 2007.
Note: The EPO treatment target Hb levels are 12 g/dl for $\mathrm{EPO_{LOW}}$, and 13 g/dl for $\mathrm{EPO_{HIGH}}$, and both strategies use the trigger level of 10 g/dl for RBCT. The RBCT strategies use trigger levels of 9, 10, and 11 g/dl, respectively.

Double EPO dose for non-responders

In the base case-analysis it was assumed that if the patient does not respond to EPO treatment during the first treatment cycle, the dose is maintained at the initial level during the second cycle and in case the patient still does not respond during the second cycle, EPO treatment is terminated. A response rate of 70% after two cycles was used. With our approach, a dose-doubling of EPO if the patient does not respond by 4 weeks, increases the response rate by 2 months to 80%. A scenario where it is assumed that if the patient does not respond during the first cycle the EPO dose is doubled during the second cycle, resulted in a cost per QALY of 35 000 EUR/QALY (322 000 SEK/QALY) compared to the $\mathrm{RBCT_{10}}$ treatment strategy. The incremental cost rises to 1 478 EUR and the QALY gain rises to 0.0407 QALYs. A comparison of this dose-doubling strategy to the fixed-dose strategy $\mathrm{EPO_{LOW}}$, however, yields a cost per QALY of 136 900 EUR (1 259 000 SEK), resulting from an incremental cost of 739 EUR and QALY gain of 0.0054.

Validation of the model against Swedish practice in 2001–2002

The primary source of data regarding Swedish treatment practice was Persson et al. [12], reflecting treatment practice in 2001 to 2002. In order to validate the model, we evaluated a four-month time frame with RBCT and EPO strategies tuned according to treatment practice at that time [12]. The model predicted the drug costs to EUR 6 087 and RBCT costs to SEK 283 by 112 days. In the study, the corresponding figures were EUR 6 152 and SEK 272 respectively, in the Eprex group. The proportion reaching a Hb level above 12 g/dl was predicted with similar precision, 32 versus 28%, and 60 versus 62%, 76 versus 79% and 81 versus 79% by 28, 56, 84 and 112 days, respectively.

Discussion

The modelled results regarding costs and effects of EPO treatment compared to treatment with RBCT correspond well to real world data regarding EPO treatment cost and effectiveness from three major hospitals in Sweden [12]. In the base case scenario, which reflects current Swedish treatment guidelines, the cost per QALY of administering EPO compared to RBCT for cancer-related anaemia falls within the range generally accepted in Sweden. The National Board of Health and Welfare [20] considers a cost of SEK < 100,000 (EUR 10 900) per QALY low (modest = SEK 100 000–500 000/QALY, high = SEK 500 000–1 000 000/QALY, very high = SEK > 1 000 000/QALY).

The cost-effectiveness of EPO treatment was compared to different strategies of treatment with RBCTs in this study. Treatment with RBCT is the most accurate alternative to EPO administration although it is not possible to, with certainty, obtain information about the exact quantities or Hb-level trigger and target levels practiced when treating anaemia with RBCTs. A modelling approach was necessary to perform analyses of different strategies. For the main comparison, complete observational data does not exist, i.e. the RBCT strategy arm had to be constructed. Varying Hb-level treatment trigger points for RBCT required a modelling approach for the same reason.

The EPO strategies differ by their target Hb level, namely 12 g/dl (EPO_{LOW}) and 13 g/dl (EPO_{HIGH}) while both use 10 g/dl as trigger level for RBCT. The main analysis in this study is between EPO_{LOW} and $RBCT_{10}$. EPO_{LOW} appears more cost-effective than all RBCT strategies. Also when comparing the EPO_{LOW} strategy to a more restrictive RBCT strategy, i.e. $RBCT_9$, the results are in favour of the EPO strategy. The incremental cost per QALY between different strategies is shown in Figure 4.

It was found to be more costly to treat patients in the initial Hb-interval 8–9 g/dl than in the initial Hb-interval 9–10 g/dl with EPO. The difference is primarily explained by a lower treatment cost and a better effect of epoetin among patients in the initial Hb-interval of 9–10 g/dl. In a systematic literature review to produce evidence-based guidelines on the use of erythropoietic proteins in anaemic patients with cancer, it was concluded that patients whose HB-level is below 9 g/dl should primarily be evaluated for need of RBCT, potentially followed by EPO treatment [5].

Practicing an EPO treatment target Hb-level of 12 g/dl yields a cost per QALY about 40% lower than practicing a Hb-target level of 13 g/dl when comparing with the $RBCT_{10}$. The incremental cost of elevating Hb-levels above 13 g/dl is very high in relation to the incremental QALY gain achieved. This finding is consistent with the updated treatment guidelines for EPO administration for cancer-related anaemia, where a Hb-target level of 12 g/dl is recommended. Also Bokemeyer et al. [5] conclude that the target Hb-level for EPO treatment should be 12–13 g/dl.

In the most recent treatment guidelines it is not recommend that the EPO dose should be doubled in non-responders [5]. This was, however, the case at the time of the observational study where the major part of the data for this study was collected [12]. Our adjustment of the response rate to reflect not doubling the dose is not based on any robust source of evidence. However, as we decreased the response rate by 10% by 2 months, where no robust evidence show a difference [5], we believe we take a conservative approach with regards to EPO response in our analyses. We find, quite expectedly, that dose-doubling is not cost-effective compared to a fixed-dose strategy.

Regarding the differences in the estimated cost-effectiveness between the NICE model and our model, there are substantial differences between the two models in terms of the models themselves, and in terms of context. The EPO treatment is performed differently in the UK compared to Sweden and this is reflected in the structures of the two models. We defined different trigger points for RBCT and will with certainty give RBCT to patients

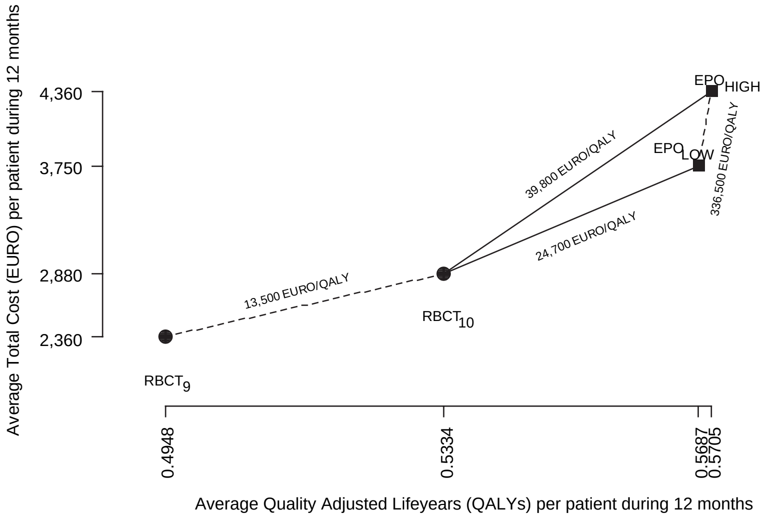

Figure 4. Cost-effectiveness of EPO and RBCT strategies; EPO_{HIGH} versus EPO_{LOW}, and both versus $RBCT_{10}$, and $RBCT_{10}$ versus $RBCT_9$.

Note: The EPO treatment target Hb levels are 12 g/dl for EPO_{LOW}, and 13 g/dl for EPO_{HIGH}, and both strategies use the trigger level of 10 g/dl for RBCT. The RBCT strategies use trigger levels of 9, and 10 g/dl, respectively.

below the trigger, while the NICE model applied a probability of RBCT under their trigger point. The NICE model uses survival benefit associated with EPO in a sensitivity analysis, while we have chosen the more conservative approach of no survival benefit for EPO. Our analysis is further on the conservative side, as we have not included the risk of adverse events associated with RBCT. Last but not least, the price of EPO and costs of blood differs between the countries.

A limitation in this study is that the cost estimates are based on budgeted unit costs derived from a hospital price lists. This is, however, an approach often used since reliable actual cost data is usually difficult to obtain. Unit costs and thereby cost-effectiveness ratios between different treatment alternatives may vary across different hospitals. Different hospitals and blood centres might use different methods for estimating and distributing e.g. over-head costs on different blood products or services. Moreover, depending on the cost perspective adapted in the analysis, costs for different factors should be included, thereby altering the results in the study. In this study, a hospital perspective was used in the cost analysis. Thus, indirect costs such as patients travel time or loss in production, associated with the different treatment alternatives was not included in the study. We have not evaluated our model using probabilistic sensitivity analysis (PSA). Although such an analysis, performed in the proper way, would provide important information, this is not required wold-wide, especially, it is not required by the Pharmaceutical Benefits Board (Läkemedelsförmånsnämnden, LFN) which decides on reimbursement in Sweden and which is currently reviewing reimbursement for anemia agents. Our model was evaluated using individually sampled initial Hb levels which should fairly well overcome the issue of uncertainty regarding this particular parameter. As mentioned before, no real-world data was available to support the RBCT treatment arm, so it had to be constructed, hence our modelling approach.

Conclusions

The estimated cost per QALY falls well within the range acceptable in Sweden when practicing a Hb-target level of 12 g/dl. The incremental cost of elevating Hb-levels above 13 g/dl is very high in relation to the incremental QALY gain achieved.

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