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ORIGINAL ARTICLE

Hemoglobin level at initiation of darbepoetin alfa: impact on need for transfusion and associated costs in chemotherapy-induced anemia treatment in Europe

Melike Deger · Wolfgang Eisterer · Lucie Kutikova · Sam Salek

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Abstract
Purpose Erythropoiesis-stimulating agents can reduce red blood cell transfusion rates in patients developing anemia while receiving chemotherapy. We investigated potential cost savings from reduced transfusion rates in patients starting darbepoetin alfa (DA) at higher versus lower hemoglobin (Hb) levels.
Methods Two systematic literature reviews were performed: transfusion outcomes in patients receiving DA stratified by baseline Hb level and costs of transfusion in Europe. Potential cost savings were calculated by multiplying the difference in transfusion rates between Hb levels by the midpoint of transfusion costs.
Results Despite differences in baseline characteristics, treatment duration and analysis technique, the clinical studies (n=8) showed that fewer transfusions were required when DA was initiated at higher versus lower Hb levels. The economic studies (n=9) showed that 1 unit of transfusion ranged from €130 to €537 (2010-adjusted values). Cost savings from initiating DA at higher versus lower Hb levels were €503–2,226 (2 units transfused) and €880–3,895 (3.5 units) per ten patients.
Conclusions Transfusion incidence increases with DA initiation at lower Hb levels. Potential cost savings depend on the number of units transfused and cost items included. DA initiation according to guidelines can reduce transfusions and potentially reduce transfusion-associated costs.

Keywords Costs · Darbepoetin alfa · Erythropoiesis-stimulating agents · Hemoglobin · Transfusion

M. Deger
Welsh School of Pharmacy, Cardiff University,
Redwood Building, King Edward VII Avenue,
Cardiff CF10 3NB, UK

M. Deger · L. Kutikova
Amgen Europe GmbH,
Dammstrasse 23,
6300 Zug, Switzerland

W. Eisterer
Department for Internal Medicine I, Medical University Innsbruck,
Anichstrasse 35,
6020 Innsbruck, Austria

S. Salek (✉)
Centre for Socioeconomic Research, Welsh School of Pharmacy,
Cardiff University,
Redwood Building, King Edward VII Avenue,
Cardiff CF10 3NB, UK
e-mail: salekss@cardiff.ac.uk

Introduction

Chemotherapy is a frequent cause of anemia in patients with cancer [1]. In this population, anemia increases the risk of death [2], and is also associated with impaired quality of life [3, 4]. Until the early 1980s, red blood cell (RBC) transfusions were the primary treatment for chemotherapy-induced anemia [5]. This changed in 1993 when the use of erythropoiesis-stimulating agents (ESAs) was approved by the US Food and Drug Administration for the treatment of anemia in patients with cancer. Approval of ESAs in Europe by the European Medicines Agency followed in 2001. Notably, ESA treatment of chemotherapy-induced anemia can reduce the requirements for RBC transfusions [6], which are associated with various risks including enhanced tumor growth, transmission of infectious diseases, and adverse reactions [1].

The goal of the treatment is improving fatigue symptoms by correcting anemia. According to current guidelines from the European Organisation for Research and Treatment of

Cancer, ESA treatment should be initiated at a hemoglobin (Hb) level of 9–11 g/dl in patients experiencing anemia-related symptoms while receiving systemic chemotherapy [6]. The European Society for Medical Oncology (ESMO) acknowledges the importance of anemia in cancer, through the negative impact upon the quality of life and as a negative prognosis factor regarding general survival [7]. ESMO recommends ESA use in the treatment of the symptomatic anemia induced by chemotherapy of adult patients with nonmyeloid malignancies with Hb values ≤10 g/dl. The goal of the treatment is improving the fatigue symptoms by correcting anemia. ASCO/ASH recommends use of ESA when Hb levels are ≤10 g/dL while considering other clinical circumstances [8]. Similarly, the European Summaries of Product Characteristics for ESAs state that treatment should be initiated when the Hb level falls to ≤10 g/dl [9–11]. In contrast, based on recent RBC transfusion guidelines [12], the recommended hemoglobin trigger for transfusion should be 7 g/dL in stable, non-bleeding patients.

Importantly, the Hb level at the time of ESA initiation may affect clinical outcomes, including RBC transfusion rates. For example, a retrospective analysis of a darbepoetin alfa (DA) study showed that the incidence of RBC transfusion was 31 % when treatment was initiated at Hb levels <10 g/dl compared with 15 % when treatment was initiated at Hb levels >10 g/dl [13]. This in turn may affect the costs of treating chemotherapy-induced anemia.

The aims of the present retrospective study were to investigate the impact of Hb level at the start of ESA treatment on the rate of RBC transfusion and to identify the potential cost-saving benefit of a reduction in transfusion rates, based on a systematic review of the literature. The present study focuses on DA, an injectable, long-acting erythropoietin with increased erythropoietin-stimulating activity relative to epoetin [14]. DA can be dosed as infrequently as once every 3 weeks, which allows treatment to be synchronized with many chemotherapy schedules [15].

Design and methods

Systematic literature review of relevant clinical studies

A systematic literature review was performed to identify articles that reported RBC transfusion rates stratified by Hb level at the time of DA initiation in patients with chemotherapy-induced anemia. To capture studies that would be in line with the most recent treatment guidelines [6], a search was conducted using the PubMed database for studies published between January 2006 and November 2010. Iterative searches were also conducted of several conference abstract databases [American Society for Clinical Oncology, American Society for Hematology, European Society for Medical Oncology (ESMO), ESMO/European Cancer Organisation and European Haematology Association joint congress] for relevant abstracts presented between 2006 and 2010. The search terms were ("darbepoetin alfa" or "darbepoetin alpha") and ("chemotherapy-induced anemia," "chemotherapy-induced anemia," or "CIA"). All articles that reported RBC transfusion rates stratified by Hb level at DA initiation in patients with chemotherapy-induced anemia were included, regardless of their study designs. Risk differences in RBC transfusion rates at different Hb stratification levels were calculated for the retrieved studies.

The summary measure to be identified by the systematic review was the risk difference in transfusion rates when DA was initiated at higher versus lower Hb levels. This was calculated [with 95 % confidence intervals (CI)] by subtracting the transfusion rate at lower Hb levels from that at higher levels.

Systematic literature review of economic studies

A second systematic literature review was performed to identify articles that reported the cost of RBC transfusion. Iterative searches were conducted using the PubMed database for studies published between November 2000 and November 2010. The following Medical Subject Heading terms were included: "blood transfusion," "autologous/economics," or "anemia/economics." The reference lists of retrieved studies from this review were scanned to identify additional articles, with no date limitation set for reference list reviewing. All articles that reported costs of RBC transfusion were included, regardless of whether they were retrospective or prospective, and whether transfusion was used in oncology or other settings. To minimize potential bias caused by differences among healthcare systems in different geographic regions, studies reporting transfusion costs in Europe were selected for further calculations.

Extracted data on costs of RBC transfusion for each article were first converted to 2010 values using consumer price index values for the relevant country [16–23]. Resulting cost was adjusted to Euro (€) values by using average 2010 currency exchange rates published by the European Central Bank [24]. Average cost per 1 RBC unit was calculated.

For studies using top-down (macro costing) methodology, unit cost was calculated by dividing the overall cost by the total number of units transfused. In studies using bottom-down (micro costing) methodology, each resource component was identified and a unit cost calculated. The overall cost of transfusion includes costs associated with blood collection and processing, as well as transfusion.

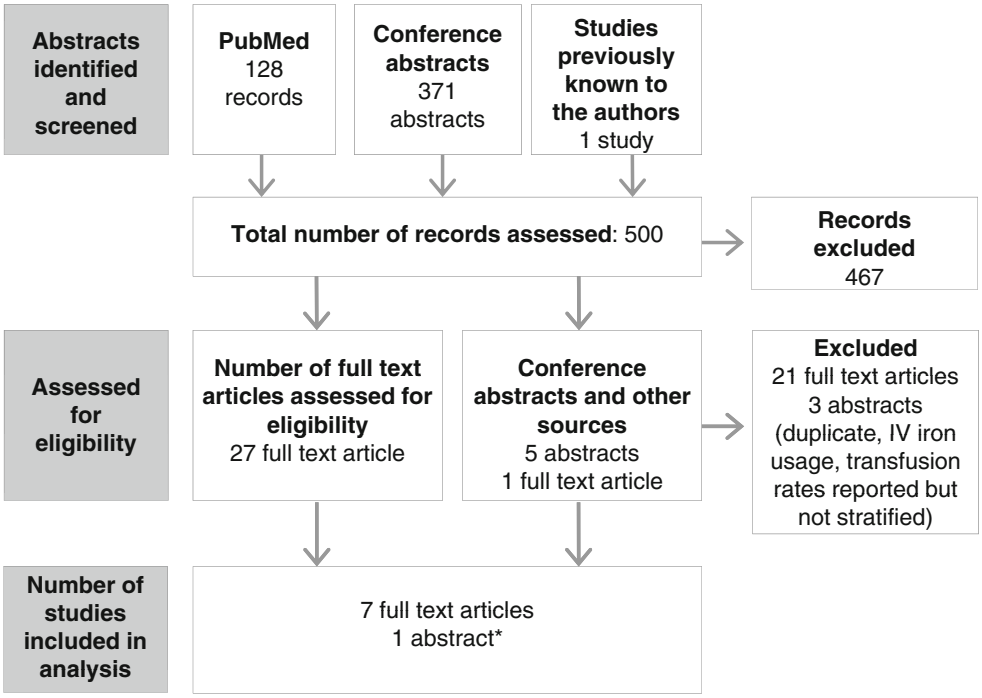

Fig. 1 Flow diagram of study selection for clinical studies. *Asterisk* two studies identified by the literature searches as conference abstracts have since been published [22, 30] and are included here as full text articles

Calculation of cost savings

To identify cost savings in the treatment of chemotherapy-induced anemia associated with Hb level at the time of DA initiation, the risk difference in RBC transfusion rates (based on that identified in the systematic review of clinical studies) was multiplied by the identified average of RBC transfusion cost in Europe (based on the systematic review of economic studies). Among the retrieved clinical studies, only one reported the actual number of units transfused (3.5 units) [25], while 2 units have been reported as an average number of units typically transfused [26, 27]. Cost savings were, therefore, calculated based on transfusion of 2 and 3.5 units of RBC.

Results

Systematic literature review of clinical studies

The initial PubMed and conference abstract searches revealed 500 potentially relevant articles, of which 27 full-text articles and 4 abstracts were assessed further for eligibility. Of these, eight publications were identified for inclusion in the clinical literature review, including seven full-text articles [25, 28–33] and one conference abstract (Fig. 1; Table 1) [34]. Five publications were based on data from clinical trials [29–31, 33, 34] and two reported results of observational studies [25, 31], with one pooled analysis of individual patient-level data from several clinical trials [32]. The eight independent studies used six different stratification levels for Hb.

Impact of hemoglobin level at DA initiation on RBC transfusion rate Despite the differences in baseline patient characteristics, dose and regimen of DA, length of study, and analytical techniques, all eight studies demonstrated a reduced need for RBC transfusion when DA was initiated at higher versus lower Hb levels.

Three studies stratified Hb at the <10 versus ≥10 g/dl level. In two, DA was administered at 300 μg every 3 weeks (Q3W) for 13 weeks [29] or 16 weeks [34], and transfusion rates were reported between weeks 5 and 16. In the third study, DA 200 μg was given Q2W for 24 weeks, and transfusion rates were reported for months 1 and 6 [25]. The risk difference in transfusion rates ranged between 16 % (95 % CI, 11–21 %) and 19 % (95 % CI, 10–28 %).

One study [30] stratified Hb at the ≤10 versus 10.5–12 g/dl level.[1] DA 300 μg was given Q3W for 22 weeks and the transfusion incidence reported as the Kaplan–Meier percentage (K–M%) for weeks 1–13. The difference in risk of transfusion was 17 % (95 % CI, 4–30 %) in favor of the higher Hb level. Another study stratified Hb at the <9 versus ≥9 g/dl level [32]. This was a 16-week prospective observational study using DA 150 μg weekly with transfusion rates reported for weeks 5–16. The risk difference for transfusion rates was 7 % (95 % CI, −5–19 %) in favor of the higher Hb level.

[1] Patients received DA immediately (Hb ≥10.5 g/dl) or waited until Hb had decreased below 10 g/dl.

Table 1 Characteristics of the eight studies identified in the systematic review of clinical studies

Study	Dose	Study design	Study design	Data source	Eligible patients	Study period (weeks)	Target Hb level (g/dl)	DA withheld (Hb; g/dl)	DA reinstated (Hb; g/dl)
Eisterer et al. 2011 [22]	500 μg Q3W	Observational	Multicenter, noninterventional, observational study, prospective	Full publication	CIA, Hb <11 g/dl	12	Hb ≥12	NR	NR
Gabrilove et al. 2007 [25]	200 μg Q2W	Clinical trial	Multicenter, open label, single arm, community based	Full publication	CIA and anemia due to cancer; Hb <11 g/dl	26	11<Hb <13	Hb ≥13	Hb ≤12
Boccia et al. 2006 [26]	300 μg Q3W	Clinical trial	Multicenter, open label, single arm, community based	Full publication	CIA and anemia due to cancer; Hb <11 g/dl	16	11<Hb <13	Hb ≥13	Hb ≤12
Charu et al. 2007 [27]	300 μg Q3W	Clinical trial	Open label, prospective, randomized,multicenter	Full publication	CIA and anemia due to cancer; 10.5<Hb <12 g/dl	22	11<Hb <13	Hb >13	Hb ≤13
Mel et al. 2008 [28]	150 μg QW	Observational	Observational, prospective, single arm, multicenter, open label	Full publication	CIA, Hb <11 g/dl	16	Hb ≥12	Hb >14	Discontinued if exceeded
Ludwig et al. 2009 [29]	Pooled analysis	Meta-analysis	Pooled analysis	Full publication	CIA	12–18	Hb ≥12	Hb >13	Hb ≤12
Canon et al. 2011 [30]	500 μg Q3W	Clinical trial	Retrospective analysis of data from a phase 3 randomized trial	Full publication	CIA, Hb <12 g/dl	15	NR	NR	NR
Malik et al. 2006 [31]	300 μg Q3W	Clinical trial	Multicenter, open label	Congress abstract	CIA; Hb <11 g/dl	16	11<Hb <13	NR	NR

Hb hemoglobin, *DA* darbepoetin alfa, *QXW* every *X* weeks, *CIA* chemotherapy-induced anemia, *NR* not reported

Two studies used three stratification levels for Hb. The first was a 15-week study with DA 500 μg Q3W in which Hb was stratified at <9, 9 to <10, and ≥10 g/dl [33]. K–M% transfusion rates were reported for weeks 1–15 and 5–15. The risk differences for weeks 1–15 were 27 % (95 % CI, 16–38 %) for intermediate versus low Hb and 16 % (95 % CI, 9–23 %) for higher versus intermediate Hb, with slightly lower risk differences when weeks 5–15 were analyzed [25 % (95 % CI, 14–36 %) and 13 % (95 % CI, 6–20 %), respectively]. The second study was an observational study using DA 500 μg Q3W, with Hb stratified at <9, 9–10, and >10 g/dl [25]. The differences in transfusion risk for weeks 1–12 were 31 % (95 % CI, 12–50 %) for intermediate versus low Hb and 9 % (95 % CI, 1–17 %) for higher versus intermediate Hb.

The final study, a pooled analysis of six studies with various DA dosing regimens, used five Hb stratification levels: <9, 9 to <10, 10 to <11, 11 to <12, and ≥12 g/dl [32]. K–M% transfusion rates were reported for week 5 to weeks 12–18. Risk differences for the four comparisons were 10 % (95 % CI, 1–19 %), 12 % (95 % CI, 5–19 %), 7 % (95 % CI, 1–13 %), and 0 % (95 % CI, –7 to 7 %), respectively.

Systematic literature review of economic studies

The initial PubMed searches revealed 286 potentially relevant articles, of which 4 met the inclusion criteria. The reference lists of these four articles were then analyzed and additional articles identified, giving a total of 21 publications that met the inclusion criteria for the economic literature reviews, of which 8 were European (Fig. 2; Table 2) [26, 27, 35–40]. One more study was identified at a later stage [41]. There were three from the UK, one each from Greece, Norway, Portugal, Spain, and Sweden, and one that included costs from Switzerland and Austria. The studies were conducted between 1998 and 2008, and all reported the actual year of the study and the actual-year costs.

Three studies assessed the cost of transfusion in an oncology setting (one in a general oncology department, one in a hemato-oncology department, and one in hematology and oncology departments), two in a surgery setting, and three in a general hospital setting, and one was a review. The costs reported in our systematic review are all allogeneic transfusion cost. The costs of transfusion were most frequently assessed from the hospitals' perspective (4/9 studies). Societal perspective was the approach in two studies, in which indirect costs such as donor productivity loss, donor transportation costs, and patient transportation costs were also considered. One study took the healthcare provider's perspective, and one took the payer's perspective.

Cost of RBC transfusion The 2010-adjusted cost of 1 unit of RBC transfusion in Europe ranged from €130 to €537 (Table 3),

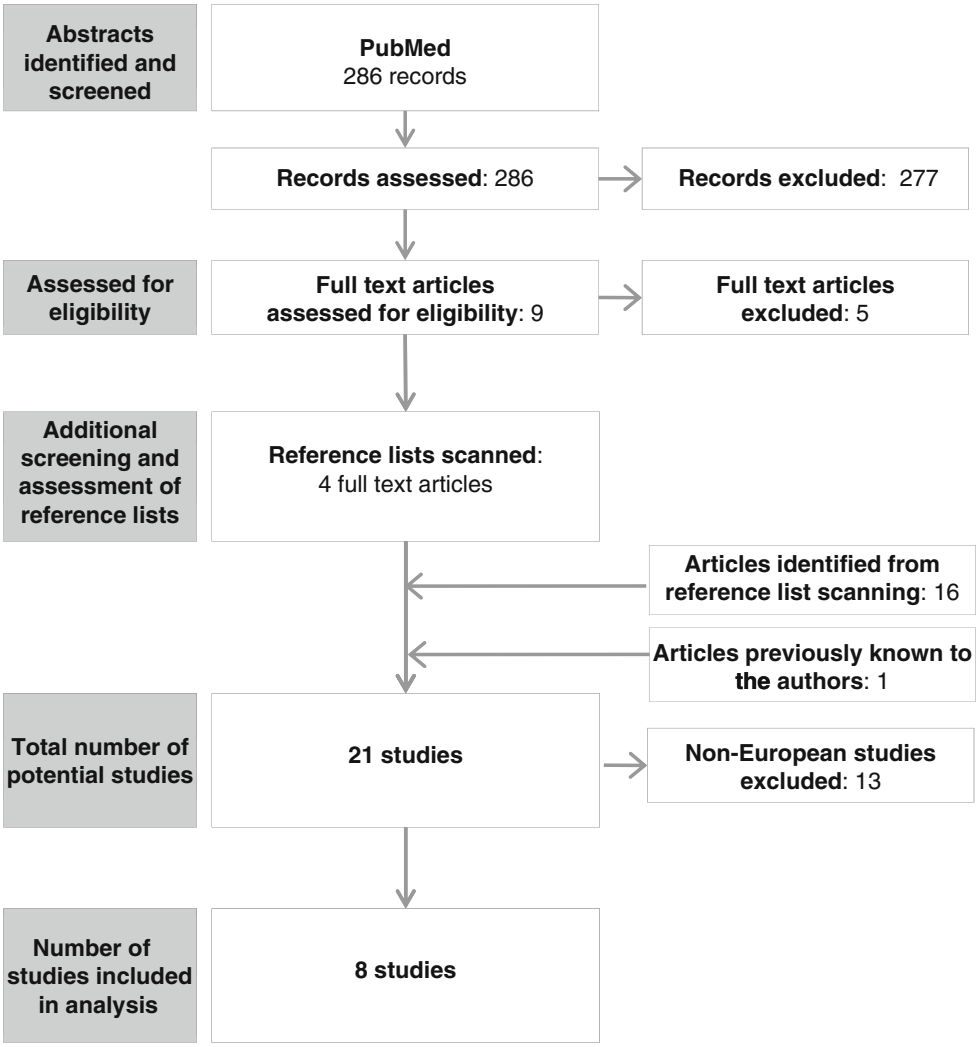

Fig. 2 Flow diagram of study selection for economic studies

with an average of €359. In general, the cost of transfusing a second unit was slightly less expensive than the first because blood grouping, Kell typing, and cross-matching of the patient only need to be performed before the initial transfusion.

Impact of baseline Hb level on cost The risk difference in transfusion rates (identified by systematic review of clinical studies) was multiplied by the midpoint of the range of cost of transfusion (identified by systematic review of economic studies). Overall, the cost savings of initiating treatment with DA at higher versus lower Hb levels ranged from €503 to €2,226 (2 units transfused) and €880 to €3,895 (3.5 units transfused) for every ten patients (Table 4). Decrease in transfusion costs could offset the increase in DA costs.

Discussion

To the best of our knowledge, the present study is the first to examine the impact of Hb level at DA initiation on the cost of treating chemotherapy-induced anemia. The findings suggest that RBC transfusion incidence decreases with higher Hb levels at the time of DA initiation and that a reduction in transfusion rate is associated with reduced costs, although the actual cost savings varied between the studies examined. Although we would have preferred to combine the studies in a meta-analysis to provide more precise estimates, the heterogeneity of the studies in terms of their study designs and reporting of transfusion rates stratified by Hb level made this impossible. It should also be noted that the measurement period of transfusion rates and the analytical method used to report transfusion rates (Kaplan–Meier or raw percentages) also varied between studies. As Kaplan–Meier estimates account for dropouts from the studies, risk differences calculated from such estimates of transfusion rates are more likely to reflect a population estimate, and cost savings calculated on this basis are, therefore, more likely to reflect real-life clinical practice.

While the present study showed that early initiation of DA can lead to a reduction in the costs associated with RBC transfusion, there are other important potential benefits from reducing transfusion rates. For example, there are risks

Table 2 Characteristics of the eight studies identified in the systematic review of economic studies

Study	Study year	Country	Setting	Study perspective	Study design	Type of costing	Units analyzed
Agrawal et al. 2006 [23]	2004	UK	Hematology/oncology	Hospital	Prospective	Bottom-up	2 units/1 unit
Glenngård et al. 2005 [24]	2002	Sweden	General	Societal	Prospective	Bottom-up	2 units/1 unit
Brilhante et al. 2008 [32]	2007	Portugal	Hemato-oncology	Hospital	Prospective	Bottom-up	2 units/1 unit
Darba et al. 2009 [33]	2002–2007	Spain	Review	Review	Review	Review	1 unit
Hadjianastassiou et al. 2002 [34]	1998–1999	UK	Surgery	Hospital	Retrospective	Bottom-up	2 units/1 unit
Kanavos et al. 2006 [35]	2004	Greece	General	Societal	Prospective	Bottom-up	1 unit
Norum and Moen 2008 [36]	2005	Norway	Oncology	Payer	Retrospective	Top-down	1 unit
Varney and Guest 2003 [37]	2000–2001	UK	General	Healthcare provider	Retrospective	Top-down	1 unit
Shander 2010	2008	Switzerland and Austria	Surgery	Hospital	Retrospective	Top-down	1 unit

associated with blood transfusions [1], and blood used for transfusion is also a scarce resource that must be managed efficiently. Thus, a reduction in transfusions may improve the efficient allocation of scarce resources. Furthermore, studies have shown that patients report a strong desire to avoid transfusions [42]. While such outcomes are beyond the scope of the present study, this preference can be measured using "willingness-to-pay" (WTP) analysis and can be included in the calculation of cost savings. The purpose of WTP measurements is to ascertain individual's maximum WTP for some—usually nonmarketed—good through hypothetical survey questions [43]. Per the recommendation of clinical guidelines, not only Hb levels but also patient symptoms and circumstances should be considered when deciding on the most appropriate treatment.

While effort should be made to reduce transfusion burden, use of ESA should follow current clinical guideline and label recommendations. Some years ago, several clinical studies and meta-analyses suggested that ESAs may reduce survival or increase disease progression [44–47]. More recent studies and meta-analyses, however, have found no negative impact upon survival [32, 48, 49]. Overall consensus has been that, when used in accordance with the prescribing information, ESA therapy is well tolerated, does not negatively affect survival, and provides important clinical benefits for patients with CIA by reducing the need for RBC transfusions and exposure to associated risks [6–11].

Previously published cost-effectiveness analyses of ESAs and RBC transfusions have generally been conducted on the basis that ESAs are an alternative to RBC transfusion, and have given conflicting results [50–52]. For example, Borget et al. [52] and Borg et al. [51] both showed that use of an ESA was cost-effective compared with RBC transfusion, while Klarenbach et al. found that ESA use was not [50]. The validity of these studies in real-life practice is, however, limited as guidelines state that ESAs and transfusions are complementary, rather than mutually exclusive, in the management of chemotherapy-induced anemia [6].

Costs of transfusion varied between countries and also from study to study, depending on the cost derivers included in the analyses and the initial economic perspective taken. While all direct labor and material costs incurred during the three main phases of the transfusion process (collection from the donor, preparation of the blood by running the

Table 3 2010 adjusted cost of 1 unit of red blood cell transfusion in Europe

Study	Cost of transfusion (reported year)	2010 values in original currencies	Adjusted 2010 values (€)
Agrawal et al. 2006 [23]	£402 (2005)	£460	€537
Glenngård et al. 2005 [24]	SEK2,243 (2003) €249	SEK2,486	€261
Brilhante et al. 2008 [32]	€349 (2007)	€357	€357
Darba et al. 2009 [33]	€350 (2007)	€370	€370
Hadjianastassiou et al. 2002 [34]	£90 (1999)	£112	€130
Kanavos et al. 2006 [35]	€355 (2004)	€433	€433
Norum and Moen 2008 [36]	NOK1,960 (2006) €240	NOK2,157	€269
Varney and Guest 2003 [37]	£235 (2001)	£286	€333
Shander 2010	$611.44 (2008)	$613	€483
	$522.45	$535	€421
Average cost			€359

NOK Norwegian Krone, *SEK* Swedish Krona

Table 4 Impact of different hemoglobin levels at darbepoetin initiation on transfusion rate and cost of treatment for chemotherapy-induced anemia

	Gabrilove et al. [25]		Boccia et al. [26]		Malik et al. [31]		Charu et al. [27]			Mel et al. [28]		Canon et al. [30]			Eisterer et al. [22]			Ludwig et al. [29]			
Time period	Month 1 (raw %)		Weeks 5–16 (raw %)		Weeks 5–16 (raw %)		Weeks 1–13 (K–M%)			Weeks 5–16 (raw %)		Weeks 1–15 (K–M%)			Weeks 1–12 (K–M%)			Weeks 1–12 (K–M%)			
Hb level at darbepoetin initiation (g/dl)	<10	≥10	<10	≥10	<10	≥10	≤10	10.5–12		<9	≥9	<9	9–<10	≥10	<9	9–10	>10	<9	9–<10	10–<11	11–<12	≥12
Transfusion rate (%)	21	4	28	12	26	7	31	14		18	11	62	35	19	50	19	10	41	31	19	12	12
Risk difference in transfusion rates (%)	17		16		19		17			7		27		16	31		9	10		12	7	0
Cost savings per 10 patients (2 units)	€1,221		€1,149		€1,364		€1,221			€503		€1,939		€1,149	€2,226		€646	€718		€862	€503	N/A
Cost savings per 10 patients (3.5 units)	€2,136		€2,010		€2,387		€2,136			€880		€3,393		€2,010	€3,895		€1,131	€1,257		€1,508	€880	N/A

Hb hemoglobin, *K–M* Kaplan–Meier, *NA* not applicable

necessary tests for safety, and transfusion to the recipient) should have been considered when reporting costs, other cost derivers are more dependent on the perspective taken.

The cost of DA treatment has been estimated at €2,094 in Belgium [53] and ranged from €1,659 to €2,378 across different European countries [54]. Considering differences in the length of treatment (12–16 weeks in clinical trials and 6 weeks in DA cost analyses), the potential cost savings of up to €3,895 for every ten patients demonstrated in the present study could be used to treat approximately one additional patient with DA. Decrease in transfusion costs could offset the increase in DA costs.

Limitations of the present study include the potential for publication selection bias arising from the use of a single publication database (PubMed). For instance, retrieved articles are highly dependent on the search strategy used, and use of multiple sources may, therefore, have reduced this effect [55]. The review of clinical studies found a trend in transfusion reduction related to Hb level at DA initiation, although it should be noted there were differences in baseline patient characteristics, lengths of the studies, and analytical techniques used to report transfusion incidence. In addition, it was assumed that the cost of RBC transfusion was constant for the first and subsequent units. The costs for the second unit of transfused blood, however, were found in some of the cited studies to be slightly less expensive than the first unit. The calculated cost savings reported here may, therefore, slightly overestimate the actual cost savings in clinical practice.

In conclusion, the findings of the clinical systematic review showed that transfusion incidence increases when DA is initiated at lower versus higher Hb levels. The cost of transfusion was found to vary from country to country and was dependent on the cost items included (e.g., direct and indirect costs). Overall, this study shows that the Hb level at DA initiation has a cost implication in the treatment of chemotherapy-induced anemia: the lower the Hb level, the greater the number of transfusions and the larger the overall cost of treatment. In patients for whom DA treatment is appropriate, treatment should, therefore, be initiated as early as possible within guideline-defined Hb levels, to reduce the need for transfusion and to decrease the overall cost of treatment. Clinical circumstances and symptoms of the patient should be considered while deciding on the most appropriate treatment of CIA.

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