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

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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

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 treatment with ESAs 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 alpha (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.
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.
| 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 arm, community based | Full publication CIA, Hb <11 g/dl | 12 | Hb ≥11 | 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 | NR | 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.
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 |
| Glennård et al. 2005 [24]                  | 2002       | Sweden  | General                  | Societal          | Prospective  | Bottom-up      | 2 units/1 unit |
| Brillante 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         |

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                     |
| Glennård et al. 2005 [24]                  | SEK2,243 (2003) £249               | SEK2,486                          | €261                     |
| Brillante 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

| Study                      | Time period | Hb level at darbepoetin initiation (g/dl) | Transfusion rate (%) | Cost savings per 10 patients (2 units) € | Cost savings per 10 patients (3.5 units) € |
|----------------------------|-------------|------------------------------------------|----------------------|----------------------------------------|------------------------------------------|
| Boccia et al. [25]         | Month 1     | <10                                       | 21                   | 1,221                                  | 2,136                                    |
|                            |             | ≥10                                       | 6                    | 2,010                                  | 2,010                                    |
| Eisterer et al. [26]        | Weeks 1–12  | <9                                        | 25                   | 1,206                                  | 1,206                                    |
|                            |             | 9–10                                     | 20                   | 1,149                                  | 1,149                                    |
|                            |             | 10–12                                    | 14                   | 1,364                                  | 1,364                                    |
| Ludwig et al. [29]          | Weeks 1–12  | <9                                        | 28                   | 1,939                                  | 3,393                                    |
|                            |             | 9–10                                     | 18                   | 2,136                                  | 2,136                                    |
|                            |             | 10–12                                    | 14                   | 2,010                                  | 2,010                                    |
| Gabrilove et al. [27]       | Weeks 5–16  | <9                                        | 25                   | 1,221                                  | 2,136                                    |
|                            |             | 9–10                                     | 20                   | 1,149                                  | 1,149                                    |
|                            |             | 10–12                                    | 14                   | 1,364                                  | 1,364                                    |
| Charu et al. [31]           | Weeks 1–13  | <9                                        | 28                   | 1,939                                  | 3,393                                    |
|                            |             | 9–10                                     | 18                   | 2,136                                  | 2,136                                    |
|                            |             | 10–12                                    | 14                   | 2,010                                  | 2,010                                    |
| Mel et al. [28]             | Weeks 5–16  | <9                                        | 28                   | 1,939                                  | 3,393                                    |
|                            |             | 9–10                                     | 18                   | 2,136                                  | 2,136                                    |
|                            |             | 10–12                                    | 14                   | 2,010                                  | 2,010                                    |
| Canon et al. [29]           | Weeks 1–15  | <9                                        | 28                   | 1,939                                  | 3,393                                    |
|                            |             | 9–10                                     | 18                   | 2,136                                  | 2,136                                    |
|                            |             | 10–12                                    | 14                   | 2,010                                  | 2,010                                    |

Hb, hemoglobin; K-M, Kaplan-Meier; N/A, not applicable.

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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