

Managing chemotherapy induced anemia with darbepoetin alfa and other erythropoiesis stimulating agents: a nurse's perspective

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Abstract: Chemotherapy induced anemia (CIA) is a frequent complication of anticancer treatment, but often remains untreated. The main presenting symptom of CIA is fatigue, and this can have profound implications upon chemotherapy treatment compliance and patients' quality of life (QoL). Nevertheless, a tendency has been seen in both patients and physicians to underestimate the consequences of fatigue. As nurses are taking on greater responsibilities for identifying, monitoring, and in some cases even treating CIA, it is important that they have a clear understanding of the treatment options at their disposal. Erythropoiesis stimulating agents (ESAs) have been available as a tool for the treatment of CIA for many years. However, the vast majority of literature on this topic has been targeted towards physicians. Hence, the purpose of this review is to summarize the key ESA studies, with an emphasis on material that is of interest to the nursing community. Herein we present a brief chronological review of the development of ESAs to illustrate how the currently available treatment options for anemia arose. For conciseness, darbepoetin alfa (DA) has been used as a model to represent all ESAs; however, important findings from studies of other ESAs have also been included for completeness. We also discuss the management of CIA, based on the available literature and our experience of routine clinical practice in the UK. In conclusion, CIA is important in the context of maintaining QoL in patients undergoing chemotherapy and its effective management needs to be considered as part of their holistic care. Available studies show that ESA treatment can decrease fatigue levels and reduce the need for transfusions. ESAs, such as DA, may therefore be an important treatment option for patients with CIA. DA is well tolerated when used according to current recommendations, can be synchronized with chemotherapy cycles, and can also be self-administered.

Keywords: chemotherapy-induced anemia, darbepoetin alfa, erythropoiesis stimulating agent, fatigue, quality of life, transfusion

Introduction

Anemia is present in approximately 50% of patients with cancer who are undergoing chemotherapy.¹ Despite this high prevalence, it may remain untreated in the majority of these patients.²

Symptoms of anemia include fatigue, weakness, shortness of breath, dizziness, and light-headedness.³ Fatigue can be particularly debilitating in patients with anemia, and has a profound impact upon their quality of life (QoL).⁴ Interestingly, around half of patients neglect to report fatigue,⁵ as they see it as a natural consequence of the chemotherapy or worry that they may be perceived as complaining. However, fatigue is associated with depression,^{6,7} a decrease in coping,⁸ a deterioration in personal relationships,⁷ and reduced treatment compliance.⁹ Therefore, treatment of fatigue

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related to chemotherapy induced anemia (CIA) is warranted – particularly as such fatigue may persist for several years after the end of chemotherapy treatment.¹⁰

Historically, CIA was treated with red blood cell (RBC) transfusions. However, due to procedure-related complications, transfusions were only used in cases of severe anemia (hemoglobin [Hb] levels ≤ 8 g/dL).¹¹ The availability of erythropoiesis stimulating agents (ESAs) provided an option for anemia management that could not only be used in previously untreated anemic patients, but could also be used to maintain target Hb levels.

A large number of studies on the effectiveness and safety of ESAs have been conducted, resulting in several adaptations of treatment guidelines. Although nurses, at least in the UK, now have more responsibility than ever before in the management of patients with CIA, the vast majority of available literature on this topic is targeted towards physicians. Hence, this review summarizes the main findings from the key ESA studies, with an emphasis on those particularly relevant to nurses. Firstly, a brief chronological review of ESA development is presented to illustrate how current treatment options for anemia arose. In this section, darbepoetin alfa (DA; Amgen Inc, Thousand Oaks, CA, USA) has been used as a model to represent all ESAs; however, important findings from studies of other ESAs have also been included for completeness. Subsequently, we will discuss the management of CIA based on the available literature and our experience of routine clinical practice in the UK.

Early 1990s to mid-2000s: development

The first recombinant human erythropoietin for the treatment of CIA, epoetin alfa (Janssen-Cilag Ltd, High Wycombe, Buckinghamshire, UK), was approved almost 20 years ago. Subsequently, epoetin beta (Roche Pharma AG, Grenzach-Wyhlen, Germany), which was biochemically different from epoetin alfa, became available. However, both ESAs are considered to belong to the same class of drug,¹² and have comparable efficacy and tolerability profiles. Both epoetin alfa and epoetin beta have been shown to be effective in correcting Hb levels and to reduce the need for RBC transfusions compared with placebo in several randomized clinical trials.¹³ The recommended dose frequency for epoetin alfa and epoetin beta was three times per week (TIW).¹⁴ When self-injection was not possible, this dosing regimen had potential to place a substantial time burden upon both patients and their health care providers – especially for those patients who otherwise did not need to be seen in the clinic so frequently.¹⁵

DA, a second generation ESA, with a different biochemical and pharmacological profile, was approved in 2002 for the treatment of CIA in patients with solid tumors in the European Union and non-myeloid malignancies in the USA using a once-weekly (QW) dose schedule. This approval was based on the results of a large phase III randomized controlled trial,¹⁶ which showed that DA QW could significantly reduce RBC transfusion requirements. Following results from two randomized controlled trials,^{17,18} DA was also approved for the treatment of CIA in patients with lymphoproliferative malignancies a year later in the European Union. The key phase III efficacy and safety studies for DA QW to every 3 weeks (Q3W) dosing schedules are summarized in Table 1.

Studies designed to investigate whether the dosing schedule of DA could be extended further then followed. Extended dosing was shown to have comparable efficacy and safety profiles to QW dosing with respect to raising Hb levels,^{19,20} and reducing RBC transfusion requirements.^{21–24} Importantly, the administration of DA Q3W represented an opportunity to synchronize ESA treatment with many chemotherapy regimens in clinical practice.²⁵ Chemotherapy has a myelosuppressive effect and as bone marrow had a hypothesized role in ESA clearance, the question was raised as to whether the efficacy of DA was different when administered synchronously or asynchronously with chemotherapy.²⁵ Further to this, a randomized clinical trial showed that the timing of DA administration relative to chemotherapy had no impact upon the resulting Hb change.²⁵ In 2005, approval of the SureClick™ device increased convenience further by allowing patients to self-inject DA. A survey has reported high levels of satisfaction with the device.²⁶ It also revealed that ease of use of the device became the main driver of satisfaction, while the importance of the pain of injection decreased over time.

The efficacy of DA, and all ESAs, is not only measured by their impact on Hb levels or RBC transfusion needs, but also by QoL. Of all of the symptoms of anemia, self-report measures indicate fatigue to have the greatest impact upon QoL.³ Therefore, the main ESA studies reporting QoL data used the Functional Assessment of Cancer Therapy (FACT)-Fatigue subscale as the primary measure of QoL. These found QoL improvements over both baseline levels^{27,28} and compared to placebo^{16,18,29} following treatment with DA.

2000–2010: long-term clinical data and updated guidelines

Despite the fact that DA showed an acceptable tolerability profile in registration studies,^{16,18} long-term clinical data

Table I Key multicenter, randomized, phase III studies investigating the efficacy and safety of various darbepoetin alfa dose schedules

DA dose schedule	Comparator	Cancer type	Number of patients	Treatment duration	Main results	Citation
2.25 µg/kg QW	Placebo	Lung	320	12 weeks	DA group needed fewer RBC transfusions and fewer units of blood; DA group had higher Hb response rate and improved QoL (FACT-Fatigue score); DA group had no adverse effect in disease outcome; AEs were similar between groups	Vansteenkiste et al ¹⁶
2.25 µg/kg QW	Placebo	Lymphoproliferative	344	12 weeks	DA group had higher Hb response rate; DA group needed fewer RBC transfusions; QoL improved in DA group; Safety profile of DA as expected	Hedenus et al ¹⁸
200 µg Q2W	EA 40,000 U QW	Non-myeloid	1,220	16 weeks	DA Q2W was non-inferior to EA QW with respect to: Need for RBC transfusions; effect on Hb levels; QoL; safety	Glaspy et al ²¹
500 µg Q3W	DA 2.25 µg/kg QW	Non-myeloid	705	15 weeks	Fewer RBC transfusions needed with DA Q3W; No differences between groups in cardiovascular/thrombotic AEs rates or safety	Canon et al ²³

Abbreviations: AE, adverse event; DA, darbepoetin alfa; EA, epoetin alfa; FACT, Functional Assessment of Cancer Therapy; Hb, hemoglobin; RBC, red blood cell; QoL, quality of life; QW, once weekly; Q2W, once every 2 weeks; Q3W, once every 3 weeks.

suggested some potential safety issues with ESAs in general, such as an increased risk of venous thromboembolism (VTE) and a potential for poorer disease control and patient survival during treatment. These concerns ultimately resulted in changes to the guidelines for ESA use and to their product labels.

Venous thromboembolism

Patients with cancer, particularly those receiving chemotherapy, are at increased risk of VTE.³⁰ A meta-analysis including data from 8,172 patients showed that this risk is further increased during ESA use (relative risk 1.57, 95% confidence interval [CI] 1.31–1.87), with 7.5% of patients receiving an ESA experiencing a VTE compared to 4.5% of placebo/standard care patients.³¹ Subsequently, the summaries of product characteristics for ESAs and relevant guidelines were updated to advise caution when ESAs are being considered for use in patients suspected to be at increased risk of thrombosis. Specific risk factors for thrombosis were not defined in these trials and so healthcare professionals should use their clinical judgment to assess this risk before prescribing ESA treatment. General risk factors for VTE that should be considered include a history of thrombosis, surgery or prolonged periods of immobilization/limited activity. Furthermore, patients with multiple myeloma treated with thalidomide or lenalidomide and doxorubicin or corticosteroids appear to be at particularly increased risk.³¹

As recommended for all hospitalized patients, patients with multiple myeloma should be assessed for their risk of developing a VTE and appropriate thromboprophylaxis (eg, aspirin or low molecular weight heparin) given as required.^{32,33}

Survival and disease progression

Rates of mortality and tumor progression in ESA-treated patients compared to controls have been analyzed in several randomized clinical trials but the impact of ESA treatment on these outcomes remains unclear. Nonetheless, eight studies reporting increased mortality and/or tumor progression in the ESA arm, have been included into the warning section of the product label for DA for the US market.^{18,34–41} Of note, four of the eight studies included patients who were not currently receiving chemotherapy (in two studies patients received an ESA, but no active chemo- or radiotherapy for their cancer;^{37,38} in another two studies, patients received radiotherapy alone).^{34,36} Concerns have also been raised over the potential impact of high target Hb levels (>12 g/dL) on survival and notably, Hb levels >12 g/dL were targeted in all of these eight studies. In contrast, an association between increased mortality and ESA use was not found in several other trials of patients with CIA, despite targeting Hb levels of >13 g/dL.^{42–45} Nevertheless, guidelines were revised to recommend target Hb levels of around 12 g/dL^{46–48} or the lowest level required to avoid transfusion (Table 2).⁴⁹

Table 2 Recommendations from oncological societies on the use of darbepoetin alfa in patients with chemotherapy-induced anemia

Society	Guidelines for DA use
EORTC ^{44,45}	Initiated at Hb levels 9–11 g/dL for CIA in symptomatic patients Target: 12 g/dL and improved symptoms
ESMO ⁴⁶	Initiated at Hb levels ≤ 10 g/dL for CIA in symptomatic patients Target: near 12 g/dL
ASH-ASCO ⁴⁷	Initiated at Hb levels ≤ 10 g/dL for CIA Target: lowest concentration required to avoid transfusion

Abbreviations: ASH, American Society of Hematology; ASCO, American Society of Clinical Oncology; CIA, chemotherapy-induced anemia; EORTC, European Organisation for the Research and Treatment of Cancer; ESMO, European Society for Medical Oncology; Hb, hemoglobin; DA, darbepoetin alfa.

Several clinical studies, reviews, and meta-analyses have attempted to clarify the effect of ESAs on survival, independent of high Hb target levels but have produced conflicting results. A review of 52 randomized controlled trials⁵⁰ and a meta-analysis of 53 randomized controlled trials⁵¹ both concluded that ESAs worsened survival. However, in the meta-analysis,⁵¹ the increased hazard ratio reported for the patients receiving concomitant chemotherapy was not statistically significant. Other meta-analyses of controlled trials within the oncological setting,^{52–54} including the largest analysis to date ($n=15,323$),⁵⁵ could find no association between ESA use and increased mortality or disease progression. Nonetheless, this led to an update of the European summary of product characteristics for DA, although no changes were made to the indication (treatment of symptomatic anemia in adult patients with non-myeloid malignancies receiving chemotherapy), which includes patients in the neoadjuvant, adjuvant and metastatic settings. However, the warnings section was revised to reflect the results of some of the studies that showed decreased survival in patients receiving ESAs, but which were conducted in settings not in line with the labeled indication. Furthermore, American Society of Oncology/American Society of Hematology guidelines⁴⁹ in the USA now advise caution in considering ESAs in patients undergoing curative-intent cancer treatment and stress the importance of a detailed discussion between healthcare providers and patients about the potential benefits and risks of ESA treatment.

2010 and beyond: The nurse's role in optimal anemia treatment with the new ESA guidelines

As an important point of contact with the patient, the nurse has great responsibility for managing CIA. He/she should

recognize the signs and symptoms of CIA, ensure appropriate treatment is initiated and administered, determine treatment response, and provide education for the patient. The preceding sections have described the use of ESAs for the treatment of mild to moderate anemia; however, the exact time point when this treatment should be initiated is still under discussion. In the UK at least, it is likely that the nurse would highlight his/her concern regarding the patient's well-being to the treating doctor/team (unless following an established clinical protocol). However, routine use of ESAs is only recommended in patients with CIA, and not with other forms of anemia.^{46–49,56}

Current guidelines state that ESA treatment should be initiated at Hb levels of 9 to ≤ 10 g/dL^{48,49} or between 9 and 11 g/dL.^{46,47} Observational studies have shown that these guidelines are generally adhered to, and that this has resulted in a well-tolerated and effective treatment of CIA.^{57–60} A retrospective data analysis⁶¹ of a large phase III trial of 706 patients with CIA aimed to assess the impact of starting ESA treatment at baseline Hb levels of <10 g/dL or ≥ 10 g/dL. The authors reported that patients who began ESA treatment with an Hb level ≥ 10 g/dL required fewer RBC transfusions and achieved a mean Hb level of 11 g/dL more quickly during the study compared to those starting treatment at Hb <10 g/dL. This result appears to be confirmed by a retrospective analysis of an observational study including 1,887 patients with cancer receiving chemotherapy and DA.⁶² Data from this study showed that faster achievement of the Hb target range (10–12 g/dL) and reduced RBC transfusion requirements were associated with the initiation of DA at Hb levels in the ranges of 9 to <10 g/dL and 10 to <11 g/dL compared to Hb <9 g/dL.⁶²

It should be kept in mind that once the decision to initiate anemia treatment has been made, it should be acted upon quickly. Recent data have shown that Hb levels of <10 g/dL drop to <9 g/dL within 6–9 weeks in about 50% of patients.^{63,64} Therefore, any delays in treatment initiation could impact patients' well-being. In this respect, regular monitoring of Hb levels and encouragement of patients to report anemia symptoms are critical. This is particularly true for patients with conditions where the Hb response to DA treatment takes longer, such as in those receiving platinum-based chemotherapy. Potential cost savings resulting from reduced RBC transfusion requirements also appear to be dependent upon the timing of DA initiation.⁶⁵

Current discussions on the appropriate treatment initiation and target Hb levels may reflect the need for a more personalized approach to the treatment of CIA. This has already

taken place in cancer treatment in general, where a patient's genetic and molecular profile are used to predict response and optimize treatment.⁶⁶ As a practical example, a patient may present with symptoms consistent with anemia and a drop in Hb levels from 15 to 11.5 g/dL. This has been described as functional anemia (Hb levels <12 g/dL) as opposed to physiologic anemia (Hb levels \leq 8 g/dL).⁶⁷ According to the guidelines, ESA treatment should not be initiated in such a patient, yet some form of intervention is clearly required because the patient has symptoms (eg, fatigue) that need to be addressed. In such a case, the first step should always be to consider other potential causes of anemia symptoms. To ensure appropriate and effective treatment for each patient, the nurse should keep in mind that the cause of anemia symptoms may not only be physiological (eg, low Hb levels), but also psychological (eg, anxiety or depression), side-effect related (eg, nausea/vomiting), comedication related (eg, side effects of other medicines), a symptom of another underlying condition (eg, pain, fever), or related to a lack of quality sleep.

What does the future hold?

In the future, it is likely that treatment for CIA will become increasingly personalized and patient-centered. As such, QoL will become even more important as an effectiveness measure. A study assessing the impact of DA on QoL when administered according to the current guidelines is in progress.⁶⁸ Treatment algorithms may also become more personalized to take into account natural inter-individual variations in Hb levels and place more emphasis on presenting symptoms and how these are affecting the patient. Considering the relatively short time span in which Hb levels can fluctuate and in which anemia can develop, it is likely that, as a primary point of contact for the patient, the nurse's role will extend to the active monitoring of patients' overall well-being.

A subgroup of patients of particular importance for further study is those aged >65 years. It is predicted that by 2050, 80% of patients with cancer will fall into this age group.⁶⁹ A recent review has summarized current knowledge in this area,⁷⁰ and reported that CIA and fatigue management in elderly patients is not considered to be a high priority by oncologists. This is despite the fact that patients of all ages with CIA are likely to benefit equally from ESA treatment.⁷⁰

Other studies currently underway will provide data on how best to individually tailor treatments towards specific patient groups. For example, the effectiveness and safety of

DA treatment in patients with myelodysplastic syndromes will be better defined following results from a European, multicenter, double-blind, placebo-controlled study that is currently being conducted.⁷¹ Another large, randomized, placebo-controlled study is focusing specifically on the use of DA in patients with non-small-cell lung cancer.⁷² Future studies may also unveil the mechanistic underpinnings of the adverse events observed in some clinical studies (increased thrombotic events and reduced survival), allowing a better understanding of how to minimize their occurrence.

For nurses, such developments are likely to lead to a greater emphasis on the effective and holistic assessment of patients receiving chemotherapy, and on monitoring their response to anemia treatment. The future may also see greater involvement of nurses not only in administering ESAs, but also in prescribing them. For example, in the UK, nurses may prescribe ESAs according to agreed protocols for patients with chronic renal disease. It remains to be seen how far this approach will spread into other indications and other countries. Although the National Institute for Health and Care Excellence (NICE) do not currently recommend the routine use of ESAs in patients with cancer in the UK, their most recent guidance was issued in 2008.⁵⁶ It will be of great interest to professionals in this field to see whether recent data have an impact on any updates to these guidelines and whether the NICE advice may change. Such developments fit well with the current emphasis on health-centered interventions during and after cancer treatment.^{73,74} In particular, encouraging results from nurse-led exercise programs on managing fatigue in patients with cancer⁷⁵ may see the role of the nurse moving from primarily administering treatment to taking responsibility for the patient's overall well-being. In such a scenario, ESAs could be a valuable tool in the nurses' repertoire.

Conclusion

Effective CIA treatment, for example, using ESAs such as DA, is important to reduce RBC transfusion requirements⁴⁶⁻⁴⁹ and improve patient QoL.⁴⁶⁻⁴⁸ DA is well tolerated when used according to current recommendations, can be synchronized with chemotherapy cycles, and can be self-administered. In the future, treatment algorithms for CIA are likely to become more personalized and a greater emphasis is likely to be placed on the active monitoring of patient wellbeing and response to anemia treatment by nurses. Considering the debilitating effects of anemia symptoms upon the patient and potentially also on cancer treatment compliance, it is likely that vigilant patient monitoring and timely intervention

by nurses would be appreciated by both patients and physicians alike.

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