Dean&Francis

ISSN 2959-409X

Retrospective Analysis Comparing the Effectiveness of Epoetin Alfa and Darbepoetin Alfa in Cancer Related and Chronic Kidney Disease Related Anemia Patients

Huiqun Qian[1, *]

[1]Department of Life Science, University of Liverpool, Liverpool, United Kingdom

*Corresponding author: hlhqian@liverpool.ac.uk

Abstract:

This retrospective analysis compares Epoetin Alfa and Darbepoetin Alfa in the treatment of patients with anaemia with cancer and anaemia with chronic kidney disease. Both erythropoiesis-stimulating agents (ESAs) stimulate erythropoiesis by modelling the natural hormone erythropoietin. Epoetin Alfa and Darbepoetin Alfa have significant structural and pharmacokinetic differences. Epoetin Alfa has a shorter half-life and needs to be administered more frequently, whereas Darbepoetin Alfa has a longer half-life and can be administered less frequently. However, they both increase the risk of thromboembolic events (TEE). This review explores the mechanisms of increased risk of TEE, evaluates clinical data, and discusses strategies to reduce risk. Clinical evidence suggests that Darbepoetin Alfa has a lower incidence of TEE compared to Epoetin Alfa. Individualisation of medication, regular haemoglobin monitoring and thromboprophylaxis in high-risk patients are essential to optimise treatment. The paper highlights the necessity of further research into safer alternatives. In summary, darbepoetin alfa may be a priority for stable patients due to its pharmacokinetic advantages and reduced risk of TEE. This article provides options to healthcare professionals for prescribing the drug and provides ideas for subsequent research directions.

Keywords: Epoetin Alfa; Darbepoetin Alfa; thrombo-embolic events (TEEs); Anemia; Cancer, Chronic Kidney Disease.

1. Introduction

Erythropoiesis-stimulating agents (ESAs), such as Epoetin Alfa, Darbepoetin Alfa, and Epoetin Beta, are drugs designed to mimic the natural hormone erythropoietin (EPO) and play a crucial role in treating anemia by stimulating red blood cell production. Epoetin Alfa and Darbepoetin Alfa, categorized as synthetic proteins, are produced through genetic engineering by inserting the human EPO gene into host cells, like Chinese hamster ovary (CHO) cells, to synthesize proteins with similar functionality to natural EPO. Epoetin Alfa has an amino acid sequence identical to human EPO, but due to its synthetic nature, it has a shorter half-life and requires more frequent administration. Darbepoetin Alfa, in contrast, is modified with additional glycosylation sites to enhance stability and extend its half-life, allowing for less frequent dosing. This recombinant protein technology enables ESAs like Epoetin Alfa and Darbepoetin Alfa to retain the biological activity of natural EPO while providing greater stability and efficacy, better meeting patients' treatment needs. Epoetin Alfa was approved by the FDA in 1985 with the trade names EPOGEN®, PROCRIT®, etc. Darbepoetin Alfa was developed to overcome some of the limitations of Epoetin Alfa. It was approved by the FDA in 2001 with the trade name Aranesp®. Epoetin Alfa and Darbepoetin Alfa promote erythrocyte division and differentiation by activating erythropoietin receptors on progenitor cells. Then increase haemoglobin levels and reduces the need for blood transfusions [1,2]. These drugs are usually used in patients with chronic kidney disease and cancer treated with chemotherapy who are less able to synthesise their own EPO. Clinical evidence suggests that such drugs can reduce anemia-related morbidity in these patients and can significantly improve their quality of life [3].

However, ESAs also increase the risk of thromboembolic events (TEEs) primarily through two factors. Firstly, the increase in hemoglobin levels caused by ESAs leads to an increase in blood viscosity. This causes a slowing of blood flow and promotes thrombosis. Secondly, ESA triggers platelet activation and enhances the expression of cell adhesion molecules on endothelial cells, which result in a hypercoagulable state [4,5]. This risk is particularly notable in patients with cancer or chronic kidney disease, where baseline risks for TEEs may already be elevated due to other factors [6]. In clinical practice, Epoetin Alfa with Darbepoetin Alfa are often used as a primary therapeutic agent for managing anemia. While both drugs are effective in raising hemoglobin levels, there are structural differences significantly impact their clinical use and effectiveness.

The purpose of this review is to explore the relationship between Epoetin Alfa, Darbepoetin Alfa and TEEs risk for Cancer Anaemia and Chronic Kidney Patients. It will examine the mechanisms contributing to the increased risk, review clinical data supporting these findings, and discuss strategies to mitigate risks while preserving the therapeutic benefits of ESA treatment.

2. Different ESAs Contributing to TEE

Epoetin alfa and darbepoetin alfa differ structurally in terms of their glycosylation patterns. Because of this, their pharmacokinetics and frequency of administration vary. Epoetin alfa is very similar to natural human erythropoietin, which is a recombinant form of human erythropoietin consisting of three N-linked carbohydrate chains. This property results in a relatively short half-life. To maintain stable hemoglobin levels in patients, especially in those with rapidly fluctuating needs due to chemotherapy or other medical conditions, the drug usually needs to be injected at a frequency of two or three times a week [7]. On the other hand, darbepoetin alfa has an extended half-life due to the addition of two carbohydrate chains, totaling five. Increased glycosylation reduces its clearance from the bloodstream, thereby greatly extending its half-life. This drug is given as often as once a week or once every two weeks to maintain normal hemoglobin levels in the body [8].

Increased blood viscosity is one of the primary mechanisms by which ESAs elevate the risk of thromboembolic events (TEEs) [9]. Increased hemoglobin usually means an increase in the number of red blood cells, which leads to an increase in blood viscosity. As blood becomes thicker, it slows circulation, especially in smaller blood vessels. facilitating clot formation within the blood vessel. In addition, at high hemoglobin levels, the increase in red blood cells may interact with platelets. This makes platelets more likely to be activated. Activation can lead to the initiation of the clotting process and increase the risk of thrombosis [10]. Supporting this link, Braekkan et al. found that each 1 g/dL increase in hemoglobin correlated with a higher incidence of venous thromboembolism particularly in men [11].

Both Epoetin alfa and Darbepoetin alfa increase hemoglobin levels. A comparative study by Locatelli et al. examined the haemoglobin response in patients with CKD treated with epoetin alfa and darbepoetin alfa [12]. They found that darbepoetin alfa (0.45 g/kg/week) was able to maintain stable hemoglobin levels with fewer doses than epoetin alfa (50UI/kg twice weekly). Similarly, darbepoetin alfa continues to be effective in raising hemoglobin levels in patients with cancer-related anemia [13]. Darbepoetin alfa's longer half-life allows it to achieve a stable,

ISSN 2959-409X

sustained hemoglobin response [14] This steadier response reduces abrupt increases in blood viscosity, which is particularly beneficial for CKD patients who face an elevated risk of cardiovascular events with fluctuating hemoglobin levels. However, the efficiency of darbepoetin alfa also poses risk. When hemoglobin rises above the recommended threshold of 2 g/dL per month, the risk of thrombosis significantly increases. Overdosing on Darbepoetin alfa, given its longer duration of action, can lead to a prolonged erythropoietic stimulus, continuously increasing blood viscosity and exacerbating TEE risks.

ESAs may also alter hemodynamic stability by increasing systemic blood pressure. The needle may cause slight damage to the lining of the blood vessel during injection. All of these causes have the potential to lead to endothelial damage and dysfunction. Endothelial cells play a critical role in maintaining vascular homeostasis, and damage to these cells may create a pro-thrombotic environment. In blood pressure, ESAs lead to increased blood pressure primarily through increased blood viscosity, which further leads to impaired endothelial function. In addition, Byrnes & Wolberg showed that ESAs inhibit the release of nitric oxide (NO) from endothelial cells and further driving up blood pressure [15]. Epoetin alfa is associated with a higher likelihood of causing hypertension, while the risk remains relatively lower with Darbepoetin alfa, though still present. This is due to the rapid onset of action and short half-life of Epoetin alfa. Palmer et al.'s data also showed that Epoetin alfa is more likely to cause hypertension compared to a placebo, with an odds ratio (OR) of 2.31, whereas Darbepoetin alfa has a slightly lower OR of 1.83. The result is significant, but there is still a large degree of uncertainty. Further experiments are needed to verify. "With Epoetin alfa, patients require more frequent injections to achieve therapeutic goals, increasing the likelihood of vascular damage at the injection site. This damage may contribute to the activation of blood clotting factors, thereby raising the risk of localized thrombosis.

3. Clinical Comparison to Assess the Association of Epoetin Alfa and Darbepoetin Alfa with TEEs

TEEs play a very important role in the treatment of anaemia in cancer patients. Treatment with erythropoiesis-stimulating agents (ESAs) significantly reduces the need for blood transfusions. In a review 6,849 breast cancer cases, only 9% patients required blood transfusion therapy after receiving ESA [16]. However, ESA therapy has also been linked to increased patient mortality. This suggests that the use of ESAs such as Epoetin alfa and Darbepoetin alfa still faces the risk of adverse effects including TEEs and potential tumor progression. Identifying the most appropriate ESA therapy is essential to protect patient safety and optimize blood supply reserves in hospitals.

Epoetin alfa considered to have higher risk of causing TEEs by some clinical data. Waltzman et al. compared the efficacy of once weekly Epoetin alfa (40,000 U) with fortnightly Darbepoetin alfa (200 μg) in 511 anaemic patients with cancer receiving chemotherapy [13]. The results demonstrated that both Epoetin alfa and Darbepoetin alfa were effective in increasing hemoglobin levels and reducing the need for blood transfusions. However, the incidence of TEEs in the Darbepoetin alfa group was only 3.9%, which was lower than the 5.7% in the Epoetin alfa group. Additional, A study by Ohashi et al. consisting of 1,800 Japanese patients, showed that the incidence of TEEs was 6.3% in the Epoetin beta group compared to 4.9% in the Darbepoetin alfa group [17]. Furthermore Sabir et al. reviewed several randomised controlled trials in breast cancer patients and found a significant increase in mortality in patients using Epoetin alfa. TEEs occurred in 5.88% of patients on Epoetin alfa and the mortality rate was a staggering 41.24%, whereas only 8.99% and 2.65% for patients using Darbepoetin Alfa respectively [16]. However, current trends have suggest that Darbepoetin Alfa may be preferable to Epoetin Alfa for the treatment of patients with cancer anaemia. Cancer patients using Epoetin Alfa need to have to deal with the risk of potential tumour proliferation, thrombosis and reduced overall survival. Therefore, doctors need to carefully assess whether to use the drug and monitor it closely when it is used.

There is no clinical evidence to suggest that Darbepoetin alfa increases the risk of TEEs. Although Bhat et al. found that the incidence of TEEs was nearly twice as high in patients treated with Darbepoetin alfa compared to those not receiving ESAs [14]. Darbepoetin alfa is still a better option for most anaemia patients with cancer and chronic kidney disease to supplement their treatment. But different treatment options still need to be considered for different patients. Some patients may have better results with Epoetin Alfa. Epoetin Alfa has a relatively short duration of action with a fast onset of action but a short duration of maintenance, making it ideal for cases where a quick increase in hemoglobin is needed, such as pre-surgical anemia correction. For those patients with more fluctuating changes in their anaemia, or who are on different treatment regimens, its short-acting nature gives doctors the flexibility to adjust the dose. Additionally, for patients with allergies to Darbepoetin alfa, Epoetin Alfa provides a viable alternative.

4. Risk Mitigation Strategies for ESAs Therapy

Therefore, effective risk mitigation strategies are essential in clinical practice to maximize treatment outcomes while minimizing potential harm associated with ESA therapy. Key strategies include individualized dosing and monitoring, thromboprophylaxis in high-risk patients, and appropriate consideration of alternative therapies.

To reduce the risk of TEEs, ESA dosing should be carefully tailored to each patient's specific needs and risk profile. Clinical guidelines consistently recommend limiting hemoglobin levels to 10-12 g/dL to effectively reduce the thromboembolism risk linked to elevated hemoglobin. Studies by Glaspy indicate that maintaining hemoglobin within this safer range prevents over-stimulation of erythropoiesis. In addition, the mortality rate of breast cancer patients is significantly higher when hemoglobin exceeds 12 g/dl, underscoring the importance of carefully managing ESA regimens [16].

Providers should proactively communicate with patients who frequently miss appointments, emphasizing the importance of consistent monitoring. Additionally, psychological support may be beneficial for patients who experience anxiety around medical visits, helping ensure adherence to regular testing.

To monitor hemoglobin levels effectively, doctors should develop a more sophisticated testing cycle. Through close observation, doctors can make the necessary dosage adjustments in time to maintain hemoglobin within target levels. This requires patient cooperation with regular testing. Healthcare providers need to communicate with patients who frequently miss appointments, emphasizing the importance of consistent monitoring. Additionally, psychological support may be beneficial for patients who experience anxiety around medical visits, helping ensure adherence to regular testing.

Individualized dosing and monitoring not only optimizes the outcome of anemia treatment, but also plays a key role in reducing ESA-related adverse effects. Especially in high-risk populations, clinicians can better balance the efficacy and safety of ESA treatment. Epoetin Alfa's fast and short acting properties make it more suitable for this purpose.

Thromboprophylaxis may be a necessary adjunct to ESA therapy in high-risk patients, especially those with a history of cardiovascular disease or previous TEEs. Despite the associated risks, anticoagulants are still beneficial for patients with advanced cancer or those receiving high-dose ESA therapy. Randomized trials of Charu et al. have shown that low-dose anticoagulants reduce the risk of TEE in these populations [18]. However, physicians need to carefully assess risk before treating with prophylactic anticoagulation methods. Such methods can significantly increase the probability of major bleeding, especially in patients undergoing concurrent surgery or invasive procedures. However, the importance of thromboprophylaxis also varies depending on the type of cancer and the choice of ESAs therapy. Darbepoetin alfa has a longer half-life and a lower incidence of TEEs than Epoetin alfa. Therefore, patients on Darbepoetin alfa may not require as aggressive thromboprophylaxis, allowing high-risk patients to undergo procedures with a reduced risk of bleeding complications.

The use of ESA therapy can place certain patients at significant risk, particularly those with cardiovascular conditions or a history of thromboembolic events. For these patients, other options for adjuvant therapy are necessary.

Acute anemia is more frequent in cancer patients than in those with chronic kidney disease. Despite the risks involved, blood transfusions are a life-saving treatment for patients in urgent need of a rapid increase in hemoglobin levels. However, repeated transfusions can lead to complications such as alloimmunization and iron overload. Additionally, for many patients, adjunctive iron supplementation is a beneficial treatment for anemia. Intravenous iron reduces the need for blood transfusions in cancer patients and greatly reduces the risks associated with full-dose ESAs therapy [19]. While these therapies reduce the exposure to TEE risk, they may bring financial burdens and social challenges for patients.

5. Future Directions in Research

Future research should focus on developing safer and more effective treatments for cancer-related anemia, building on decades of evidence supporting the efficacy of Epoetin Alfa and Darbepoetin Alfa. Despite their benefits, ESAs carry risks, particularly regarding thromboembolism, underscoring the need for alternative therapies that stimulate erythropoiesis without these risks. In 2023, the FDA approved a new drug called Jesduvroq, the first oral medication for the treatment of anaemia caused by chronic kidney disease [20]. Jesduvroq could stabilize the Hypoxia-Inducible Factor (HIF) complex by inhibiting Hypoxia-Inducible Factor Prolyl Hydroxylase Inhibitor (HIF-PHI), which promotes endogenous EPO production [21]. The treatment offers patients a non-invasive alternative to ESAs therapy and minimizes the likelihood of the patient having TEEs as a result of the injection. However, due to its relatively low absorption rate, Jesduvroq requires daily ingestion to maintain effective blood concentrations. For patients with severe anemia, the high cost—over $50 per day at the maximum 12mg dose—can impose a signifi-

ISSN 2959-409X

cant financial burden. Additionally, despite its benefits, the drug still carries a risk of hypertension and thromboembolic events. Physicians should carefully weigh the patient's physical condition and economic capacity when determining the most suitable treatment strategy.

6. Conclusion

In conclusion, clinical evidence suggests that Darbepoetin Alfa may be the preferred treatment for cancer- and CKD-related anemia due to its favorable pharmacokinetics and less frequent dosing, which is beneficial for stable patients. Both Darbepoetin Alfa and Epoetin Alfa effectively reduce the need for transfusions but increase the risk of TEEs, particularly in high-risk patients. Tailored treatment, regular hemoglobin monitoring, and anticoagulation for at-risk patients are essential to minimizing these risks. Future research should focus on personalized approaches and improved drug delivery to make anemia treatment safer and more affordable. Additionally, further data collection on treatment costs and comparative outcomes would provide valuable insights into cost-effective anemia management.

References

[1] Locatelli F, Canaud B. Dialysis adequacy today: a European perspective. Nephrology Dialysis Transplantation. 2012 Aug 1;27(8):3043-8.

[2] Stauffer ME, Fan T. Prevalence of anemia in chronic kidney disease in the United States. PloS one. 2014 Jan 2;9(1):e84943.

[3] Evans M, Bower H, Cockburn E, Jacobson SH, Barany P, Carrero JJ. Contemporary management of anaemia, erythropoietin resistance and cardiovascular risk in patients with advanced chronic kidney disease: a nationwide analysis. Clinical kidney journal. 2020 Oct;13(5):821-7.

[4] Wanchoo R, Jhaveri KD, Fishbane S. Treatment with Erythropoiesis Stimulating Agents in Patients with Chronic Kidney Disease Complicated by Cancer. Journal of Onco-Nephrology. 2017 May;1(2):81-6.

[5] Corinaldesi G. Platelet activation in cardiovascular disease. Blood. 2011 Nov 18;118(21):5242.

[6] Fishbane S. The role of erythropoiesis-stimulating agents in the treatment of anemia. Am J Manag Care. 2010 Mar 1;16(Suppl Issues):S67-73.

[7] Allen G, Kruger A, Juneja R, Passaris G, Barbara JA. Improved haemoglobin levels with reduced frequency of administration of epoetin alfa. Renal Society of Australasia Journal. 2012 Nov 1;8(3):158.

[8] Vanrenterghem Y, Barany P, Mann JF, Kerr PG, Wilson J, Baker NF, Gray SJ, European/Australian NESP 970200 Study Group. Randomized trial of darbepoetin alfa for treatment of renal anemia at a reduced dose frequency compared with rHuEPO in dialysis patients. Kidney international. 2002 Dec 1;62(6):2167-75.

[9] Fibben KS, Lam WA, Zhang DY, Kemp ML, Wood DK, Eiffrig E. Visualizing Sickle Cell Disease Whole Blood Flow and Viscosity through Modifications to Hemoglobin Levels from a Simple Blood Transfusion. Blood. 2021 Nov 23;138:3244.

[10] Barbui T, Finazzi G, Falanga A. Myeloproliferative neoplasms and thrombosis. Blood, The Journal of the American Society of Hematology. 2013 Sep 26;122(13):2176-84.

[11] Brækkan SK, Mathiesen EB, Njølstad I, Wilsgaard T, Hansen JB. Hematocrit and risk of venous thromboembolism in a general population. The Tromsø study. haematologica. 2010 Feb;95(2):270.

[12] Locatelli F, Olivares J, Walker R, Wilkie M, Jenkins B, Dewey C, Gray SJ, European/Australian NESP 980202 Study Group. Novel erythropoiesis stimulating protein for treatment of anemia in chronic renal insufficiency. Kidney international. 2001 Aug 1;60(2):741-7.

[13] Waltzman R, Croot C, Justice GR, Fesen MR, Charu V, Williams D. Randomized comparison of epoetin alfa (40,000 U weekly) and darbepoetin alfa (200 μg every 2 weeks) in anemic patients with cancer receiving chemotherapy. The Oncologist. 2005 Sep 1;10(8):642-50.

[14] Bhat S, Nguyen K, Yee J, Besarab A, Poirier W, Frinak S, Holcomb J. 28: Efficacy of Darbepoetin Alfa (DA) in Hemodialysis (HD) Patients. American Journal of Kidney Diseases. 2008;4(51):B34.

[15] Byrnes JR, Wolberg AS. Red blood cells in thrombosis. Blood, The Journal of the American Society of Hematology. 2017 Oct 19;130(16):1795-9.

[16] Sabir S, Khan YH, Khatoon M, Noreen R, Mallhi TH, Jabeen N. Effect of erythropoiesis stimulating agents on clinical outcomes in breast cancer patients: A systematic review of randomised controlled trials. J Coll Physicians Surg Pak. 2020 Mar 1;30(3):292-8.

[17] Ohashi Y, Uemura Y, Fujisaka Y, Sugiyama T, Ohmatsu H, Katsumata N, Okamoto R, Saijo N, Hotta T. Meta-analysis of epoetin beta and darbepoetin alfa treatment for chemotherapy-induced anemia and mortality: Individual patient data from J apanese randomized, placebo-controlled trials. Cancer Science. 2013 Apr;104(4):481-5.

[18] Charu V, Belani CP, Gill AN, Bhatt M, Tomita D, Rossi G, Ben-Jacob A. Efficacy and safety of every-2-week darbepoetin alfa in patients with anemia of cancer: a controlled, randomized, open-label phase II trial. The Oncologist. 2007 Jun 1;12(6):727-37.

[19] Glaspy JA, Lim-Watson MZ, Libre MA, Karkare SS, Hadker N, Bajic-Lucas A, Strauss WE, Dahl NV. Hypophosphatemia associated with intravenous iron therapies for iron deficiency anemia: a systematic literature review. Therapeutics and Clinical Risk Management. 2020 Apr 8:245-59.

[20] Park B. Jesduvroq Approved for Anemia of CKD in Patients on Dialysis. Clinical Advisor. 2023 Feb 7:NA-.
[21] T-Cells CA. 2023. Jesduvroq (daprodustat) approved by US FDA for anaemia of chronic kidney disease in adults on dialysis. Retrieved from [https://www.gsk.com/en-gb/media/press-releases/jesduvroq-daprodustat-approved-by-us-fda-for-anaemia-of-chronic-kidney-disease-in-adults-on-dialysis/]