**Editorial Commentary** | Oncology: Other



# Erithropoiesis stimulating agents in the treatment of chemotherapy induced anemia: what do guidelines say?

**Alfredo Tartarone[1]^, Rosa Lerose[2], Marina Tartarone[3]**

[1]Department of Onco-Hematology, Division of Medical Oncology, IRCCS-CROB Referral Cancer Center of Basilicata, Rionero in Vulture, PZ, Italy; [2]Hospital Pharmacy, IRCCS-CROB Referral Cancer Center of Basilicata, Rionero in Vulture, PZ, Italy; [3]Faculty of Medicine, Humanitas University, Rozzano, MI, Italy

*Correspondence to:* Alfredo Tartarone, MD. Department of Onco-Hematology, Division of Medical Oncology, IRCCS-CROB Referral Cancer Center of Basilicata, via Padre Pio 1, 85028 Rionero in Vulture, PZ, Italy. Email: tarta1@virgilio.it.

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Anemia, defined as a condition in which the red blood cells (RBCs) count or the hemoglobin (Hb) concentration are below normal levels, is a common condition in cancer patients, affecting around 40% of patients at diagnosis and up to 80% of patients undergoing anticancer therapy (1). The cause of anemia in cancer patients is multifactorial, with factors such as the malignancy itself, blood loss, cancer treatment, nutritional deficiencies, older age, concomitant diseases, hemolysis, or inflammatory cytokines associated with chronic disease contributing to its development. According to the common toxicity criteria of the National Cancer Institute (NCI), grading of anemia is as follows: mild (Hb 10.0 g/dL to lower limit of normal), moderate (Hb 8.0 to 10.0 g/dL), severe (Hb 6.5 to 7.9 g/dL), life-threatening (Hb less than 6.5 g/dL) (2). All anemia-related symptoms (pallor, headache, anorexia, breathlessness, tachycardia, menstrual disorders, decreased libido, etc.) exert an adverse impact on quality of life (QOL) of the patients. Additionally, anemia plays a central role in the pathogenesis of fatigue in cancer patients, which is characterized by a persistent subjective sense of tiredness that interferes with daily activities (3). The severity and incidence of chemotherapy induced anemia (CIA) depend on many factors, including the type of chemotherapy regimens administered and whether the patient is treatment-naïve or pretreated. Xu *et al.* using data from the integrated Kaiser Permanente Southern California health plan conducted a retrospective study to evaluate and characterize the risk of CIA among 4,426 patients with five common types of solid tumors (lung, breast, colorectal, ovary and stomach) diagnosed in 2010–2012 (4). The authors reported that 3,962 (89.5%) patients developed CIA (58% grade 1, 34% grade 2, 8% grade 3, 1% grade 4), that the incidence of anemia varied significantly across chemotherapy regimens ranging from about 18% in breast cancer patients treated with cyclophosphamide + docetaxel to about 60% in ovarian cancer patients receiving carboplatin + paclitaxel and that the risk of anemia was greater in patients with more advanced disease. The European Cancer Anaemia Survey (ECAS) evaluated the incidence, prevalence and treatment of anemia in about 15,000 cancer patients of which 6,831 were in treatment with chemotherapy, radiotherapy or concomitant chemoradiotherapy (5). The results showed that prevalence of anemia at enrolment was 39.3%, incidence of anemia was 53.7% and that anemia was treated in 38.9% of patients respectively with erythropoietin (EPO) 17.4%, RBCs transfusion 14.9% and iron 6.5%. CIA can be corrected through either transfusion of RBCs or administration of erythropoiesis-stimulating agents (ESAs), e.g., epoetin alfa, epoetin beta, darbepoetin alfa etc. with or without iron supplementation. However, if other causes of anemia are present, they should be addressed. Current guidelines

^ ORCID: 0000-0002-0859-7847.

**Table 1** Possible causes of non-response to ESAs

| |
|---|
| Blood loss |
| Iron deficiency |
| Vitamin B12/folate deficiency |
| Infection |
| Myelodysplastic syndrome |
| Bone marrow fibrosis |
| Anti-erythropoietin antibodies, pure red cell aplasia |
| Non-compliance of patients |

ESAs, erythropoiesis-stimulating agents.

recommend RBC transfusion as the best option for patients with Hb <8 g/dL who require a quick correction of anemia, while ESA therapy should be considered in patients under chemotherapy with an Hb level <10 g/dL (6-9). As described below, in case of iron or vitamin B12 or folate deficiency a corresponding replacement therapy should be administered. However, in the management of these patients we should keep in mind that ESAs are effective in about 60% of cases and should be used with caution in patients at risk of venous thromboembolism (VTE) (*Table 1*). For this reason, several risk scores for predicting VTE have been developed (6).

In this context, we reviewed the role of ESAs in the treatment of CIA in cancer patients, examining the differences between the main available guidelines.

Over a century ago, Paul Carnot and Clotilde-Camille Deflandre, two French researchers, observed that injecting a small amount of serum obtained from previously bled rabbits into normal rabbits resulted in an increase in the production of RBCs within a few hours. They hypothesized that this was due to the presence of a humoral factor, which they named "hemopoietine", that was produced in response to anemia. Subsequent investigations revealed that this factor was an amino acid glycoprotein hormone synthesized and secreted by the kidneys, which was named EPO. EPO stimulates the production of RBCs in the bone marrow in response to cellular hypoxia by binding to EPO receptors and activating JAK-STAT (signal transducers and activators of transcription) signaling pathways within the cytosol (10-12).

Recombinant EPO (rhEPO) is an artificial version of natural EPO, produced in laboratory by cloning the EPO gene, that has the same amino acid sequence, mechanism of action, and functions. Epoetin alfa, a 165-amino acid erythropoiesis-stimulating glycoprotein produced using recombinant DNA technology, received U.S. Food and Drug Administration (FDA) approval in June 1989 for the treatment of anemia secondary to chronic kidney disease and in 1993 for the treatment of CIA, followed by beta formulations. It has become one of the most widely used drugs developed through recombinant DNA technology. Epoetin beta (Neorecormon®) is a recombinant form of EPO that is similar in function and efficacy to epoetin alfa but has a longer half-life (13). Since 1997 it has been licensed in Europe to treat CIA. Darbepoetin alfa (Aranesp®) is a recombinant erythropoietic protein that requires fewer injections than previous treatments used for this indication. In fact, due to its increased sialic acid-containing carbohydrate content, darbepoetin alfa has a 3-fold longer circulating half-life than epoetin alfa, thus allowing to treat anemia with less-frequent injections than the current standard of care (14). Darbepoetin alfa was initially approved by the FDA in September 2001, for the treatment of anemia secondary to chronic kidney disease in patients who may or may not be on dialysis and on March 2006 for the treatment of CIA. In June 2001 darbepoetin alfa was approved by the European Medical Agency (EMA) for the treatment of anemia secondary to chronic kidney disease and of CIA in adult cancer patients with non-myeloid malignancies. Darbepoetin alfa sometimes causes seizures, especially during the first few months of treatment, therefore it should be used with caution in patients with history of seizure. In 2007, the EMA approved HX575 (Binocrit®), the first EPO alfa biosimilar to treat anemia caused by chronic kidney disease or chemotherapy (15). The FDA also approved this drug in May 2018. When a biological product's patent expires, a biosimilar alternative can be developed. This alternative has similar safety, efficacy, and biological activity to the original product, but at a lower cost. Developing a biosimilar involves demonstrating its comparability to the original product, including phase I pharmacokinetics and pharmacodynamics studies to show bioequivalence, and a phase III trial to confirm that there are no clinical differences compared to the reference drug. For example, in the phase III confirmatory study of HX575 (Binocrit®) 74 patients were randomized to treatment with HX575 (Binocrit®) and 40 patients to the treatment with the reference drug (epoetin alfa) (16). In patients treated with HX575 (Binocrit®), haemoglobin increased at least 2 g/dL from baseline in 62% of cases and the confidence interval was entirely above the pre-defined 30% threshold; both groups showed similar results in terms of safety and secondary efficacy parameters such as RBC transfusion requirements (32% *vs.* 38%).

**Table 2** Epoetin and darbepoetin alfa: a comparison between FDA and EMA approved indications

| Drug | FDA indications | EMA indications |
|---|---|---|
| Epoetin alfa | Anemia secondary to chronic kidney disease; zidovudine-induced anemia in HIV patients; CIA in patients with cancer (non-myeloid malignancies); reduction of blood transfusions in patients undergoing elective, nonvascular, noncardiac surgery | Anemia secondary to chronic kidney disease; CIA in patients with cancer and to reduce the need for blood transfusions; to allow autologous blood transfusions in adult patients with moderate anemia and normal blood iron levels before surgery; to reduce blood transfusions in patients with moderate anemia undergoing major orthopaedic surgery; anemia in adults with myelodysplastic syndromes |
| Darbepoetin alfa | Anemia secondary to chronic kidney disease; anemia secondary to concomitant myelosuppressive chemotherapy | Anemia secondary to chronic kidney disease; CIA in patients with cancer (non-myeloid malignancies) |

FDA, Food and Drug Administration; EMA, European Medicines Agency; HIV, human immunodeficiency virus; CIA, chemotherapy induced anemia.

*Table 2* reports a comparison between FDA and EMA approved indications for epoetin and darbepoetin alfa. Epoetin zeta (Retacrit®) represents another EPO alfa biosimilar available for the treatment of anemia caused by chronic kidney disease or chemotherapy. In 2008, a meta-analysis published by Bennett *et al.* including 51 phase 3 trials with 13,611 patients that included survival information and 38 trials with 8,172 patients that included information on VTE showed that ESAs use in cancer patients was associated with an increased risk of VTE (334 VTE events among 4,610 patients treated with ESA *vs.* 173 events among 3,562 control patients) and mortality [hazard ratio (HR) =1.10; 95% confidence interval (CI), 1.01–1.20] (17). In 2009 another meta-analysis, that analysed data of 13,933 cancer patients extracted from 53 phase III trials, in which ESAs plus RBC transfusions were compared with transfusion alone for prophylaxis or treatment of anemia in cancer patients (18). The authors concluded that the use of ESAs increases mortality during the study period and worsens overall survival. A subsequent Cochrane systematic review including 91 trials with 20,102 participants evaluating the use of ESAs to prevent or reduce anemia in cancer patients treated with chemotherapy, radiotherapy or chemoradiotherapy (19) indicated that the use of ESAs reduces RBC transfusions and improve QOL, but increases risk of VTE, hypertension and mortality (19). Authors concluded that in this clinical setting the increased risk of VTE and death should be balanced against the potential benefits of ESAs administration. However, the previously reported meta-analyses had several flaws: for example, with few exceptions, study outcomes were underreported leading to overestimates of both positive and negative effects of ESAs as well as another bias could be the inclusion of studies in which ESAs had been used outside of their indications. In any case in response to these alerts, in 2010 the FDA started a Risk Evaluation and Mitigation Strategy (REMS) called ESA APPRISE program to ensure that the benefits for use of ESAS as treatment of CIA outweighed the risks including thromboembolism, stroke, cardiovascular events, shortened overall survival and increased likelihood of recurrence and tumor progression in cancer patients. In April 2017, the FDA ended the ESA APPRISE REMS program after determining that physicians understood the previously mentioned risks and were prescribing ESAS appropriately according to current clinical guidelines. In 2014 and 2018 also the UK National Institute for Health and Care Excellence (NICE) confirmed that ESAs are recommended, within their marketing authorisations, for the treatment of CIA.

The main current guidelines say that: in patients with mild CIA (Hb 10–11.9 g/dL) the use of ESAS is not recommended; in case of iron deficiency (ID), characterized by transferrin saturation (TSAT) <20% or serum ferritin (SF) <100 ng/mL, iron therapy should be administered, preferably intravenous (IV); in presence of vitamin B12 or folate deficiency replacement therapy with vitamin B12 or folate should be provided; in patients with moderate CIA (Hb 8.0–9.9 g/dL) the administration of ESAs is recommended, while patients with severe CIA (Hb <8 g/dL) should receive RBCs transfusions (6-9).

A Cochrane systematic review including 8 studies (2,087 participants) compared ESA plus iron supplementation *vs.* ESA alone in patients with CIA (20). The study indicated that addition of iron to ESAs improves Hb levels and reduces the need for RBCs transfusions. The subgroup analyses suggested the superiority of parenteral iron over oral iron supplementation. Another large European patient record study showed that iron status had been assessed (by SF)

 

**Table 3** What do the guidelines say about the use of ESAs in cancer patients?

| Clinical question | ASCO/ASH 2019 guidelines (6) | NCCN guidelines (v.1.2023) (8) | ESMO guidelines 2018 (7) | AIOM guidelines 2021 (9) |
|---|---|---|---|---|
| ESAs are indicated for | Patients with CIA whose cancer treatment is not curative in intent and whose Hb has declined to <10 g/dL | Patients with CIA undergoing palliative treatment according to FDA approved indications/ dosing/dosing adjustments | Patients with CIA with an Hb level <10 g/dL | Patients with CIA with an Hb level ≤10 g/dL |
| ESA dosing modifications | Starting and modifying doses follow FDA guidelines | Starting and modifying doses follow FDA guidelines | Dosing follows the approved labels; dose escalations in patients not responding within 4–8 weeks are not recommended | Dose escalation ± iron therapy is allowed in patients not responding within 4 weeks; revaluation of Hb levels at 8 weeks |
| Hb target | Hb may be increased to the lowest concentration needed to avoid or reduce the need for RBC transfusions | No Hb target is mentioned | The Hb target is 12 g/dL | The Hb target is 12 g/dL |
| Response to treatment | ESAs should be discontinued in individuals who do not respond within 6–8 weeks | ESAs should be discontinued in individuals who do not respond within 8 weeks despite iron supplementation | ESAs should be discontinued in individuals who do not respond within 8 weeks | ESAs should be discontinued in individuals who do not respond within 8 weeks |
| Iron | Iron replacement may be used | Consider IV or oral iron supplementation in case of absolute iron deficiency; consider IV or iron supplementation with ESAs in case of functional iron deficiency | Consider IV iron supplementation ± ESAs in case of absolute iron deficiency; consider IV iron supplementation with ESAs in case of functional iron deficiency | Consider IV iron supplementation ± ESAs in case of absolute iron deficiency; consider IV iron supplementation with ESAs in case of functional iron deficiency |

Absolute iron deficiency: serum ferritin <30 ng/mL and transferrin saturation <20%; functional iron deficiency: transferrin saturation <50% and serum ferritin 30–500 ng/mL. ESAs, erythropoiesis-stimulating agents; ASCO, American Society of Clinical Oncology; ASH, American Society of Hematology; NCCN, National Comprehensive Cancer Network; ESMO, European Society of Medical Oncology; AIOM, Italian Association of Medical Oncology; CIA, chemotherapy induced anemia; FDA, Food and Drug Administration; Hb, hemoglobin; RBC, red blood cell; IV, intravenous.

only in half of the patients treated for CIA and despite the evidence of ID in 42% of patients iron supplementation was only used in 31% of them, with oral administration in the majority of cases (74% oral, 26% IV iron) (21). Also, the Italian retrospective ANEMONE study, that investigated the effect of biosimilar epoetin alfa in anaemic cancer patients, showed a relatively low use of iron supplementation (22).

In contrast to the amount of clinical evidence available, iron treatment is often inadequately utilized and typically involves oral iron supplementation. Unfortunately, due to the commonly elevated levels of hepcidin in cancer patients, which impede the function of ferroportin, the iron transporter responsible for moving iron from enterocytes into the bloodstream, orally administered iron may be less effective than its IV counterpart. However, a recent innovation in the form of oral sucrosomial iron, which boasts superior bioavailability when compared to traditional oral formulations, could represent a promising therapeutic option for addressing ID (23).

Despite the recognized role of ESAs in treating CIA, some disparities exist among the main available guidelines. For instance, while the American Society of Clinical Oncology/American Society of Hematology (ASCO/ASH) and the National Comprehensive Cancer Network (NCCN) guidelines suggest that ESAs may be offered to patients with CIA (Hb <10 g/dL) whose cancer treatment is not curative in intent, the European Society of Medical Oncology (ESMO) and the Italian Association of Medical Oncology (AIOM) guidelines recommend ESAs for all patients with CIA (Hb <10 g/dL) (6-9).

*Table 3* summarizes what the guidelines say about the use of ESAs in cancer patients.

In conclusion, ESAs have been shown to be highly effective in managing CIA, as evidenced by numerous studies (24,25). Guidelines and recommendations have been developed to ensure the optimal use of these therapies, while also considering their cost-benefit balance. However, there are some discrepancies among these guidelines, as highlighted earlier. Specifically, according to the ASCO/ASH and NCCN guidelines, ESAs should only be offered to patients with CIA (Hb <10 g/dL) whose cancer treatment is not curative in intent, whereas the ESMO/AIOM guidelines recommend ESAs treatment for all patients with CIA (Hb <10 g/dL) (6-9). Epoetin beta, epoetin alfa, darbepoetin alfa, and biosimilar epoetin alfa have shown similar efficacy and safety profiles, and there is currently no clinical evidence suggesting that ESAs stimulate relapse or disease progression when used according to label instructions and recommendations for the treatment of CIA (6,7). When treating CIA, iron status (ferritin and TSAT) should be evaluated, and IV iron should be used in conjunction with ESAs as necessary. Additionally, caution should be exercised when administering ESAs to patients at risk of VTE (such as those who have undergone surgery or are immobilized).

Given the heterogeneity of cancer patients, it is important that management of CIA be provided by physicians with expertise in this field.

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