# Current trends in the management of anaemia in solid tumours and haematological malignancies

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**Purpose of review**
Anaemia is a common problem in patients with solid tumors and haematological malignancies. Certain cancer therapies also contribute to anaemia. This article reviews the pathophysiology of cancer-related anaemia, investigation of a cancer patient with anaemia as well as how anaemia impacts patients in terms of quality of life, disease-related outcomes and treatment choices.

**Recent findings**
Different treatments for anaemia include transfusions, erythropoiesis-stimulating agents (ESA) and iron therapy. Within this context, we review the advantages and disadvantages concerning anaemia management in cancer patients as well as the risk–benefit ratio of different treatment choices, particularly the increased risk of thromboembolic events of ESAs and concern around mortality and effect on tumor growth.

**Summary**
This review is aimed at guiding treating physicians to make the best evidence-based treatment choices according to the product label and according to current guidelines for patients with cancer-related anaemia.

**Keywords**
anaemia, cancer, cancer-related fatigue, erythropoiesis stimulating agents, iron therapy

## INTRODUCTION

Symptoms of anaemia are often the index presentation in patients with cancer. Of these patients, symptoms occur in about 60–70% with haematological malignancies and in about 40% of patients with solid tumours. Furthermore, 30% will have mild anaemia, 9% will have moderate anaemia, and 1% will have severe anaemia. According to the National Cancer Institute, mild anaemia is defined as a haemoglobin level between 9.5–10.9 g/dl, moderate anaemia between 8.0 and 9.4 g/dl and severe anaemia between 6.5–7.9 g/dl. Life-threatening anaemia is found at levels less than 6.5 g/dl (Table 2). There is controversy around what prognostic implications cancer-related anaemia (CRA) has on patients. Anaemia has been associated with a shorter survival and an increased relative risk of death in patients, in several different malignancies. Treating and correcting the underlying anaemia in patients with cancer is said to improve outcome [1].

The treatment administrated for the underlying cancer, further complicates or worsens CRA. The overall incidence of chemotherapy and radiation-induced anaemia is 54% [2]. The nephrotoxic effects of chemotherapy agents such as cisplatin can be associated with the persistence of anaemia through reduced renal production of erythropoietin. The cause of CRA is multifactorial and can be categorized into different groups, including blood loss, increased destruction, and decreased production of red blood cells (Table 1). Often the various mechanisms responsible for causing CRA are connected. The severity of CRA is graded according to the National Cancer Institute (Table 2) [2–4].

## TEXT OF REVIEW

### Epidemiology and aetiology of anaemia in cancer

The European Cancer Anaemia Survey assessed the epidemiology of anaemia in patients with cancer. The European Cancer Anaemia Survey trial was a

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## KEY POINTS

- ESAs increase haemoglobin levels, reduce transfusion requirements, and improve the QOL.
- ESAs increase the risk of thromboembolism and may be associated with a shorter time to cancer progression.
- ESAs should be used according to current treatment guidelines and product label.
- Blood transfusions are efficient especially when there is a need for immediate increases in haemoglobin levels.

large, prospective study of 15 367 patients, which allowed patients with any stage of cancer, and also patients who had received any type of anticancer treatment. The study looked at predominately women with breast cancer (30.4%) or gynaecological cancer (49.1%). Approximately 40% of patients had haemoglobin levels lower than 12 g/dl. Of the patients receiving chemotherapy, 75% developed anaemia within 6 months. Independent factors associated with the development of anaemia were the baseline level of haemoglobin, the site of the primary tumour, the use of platinum-containing regimens, female gender, advanced age, and low performance status [5].

**Table 1.** Causes of anaemia in cancer

| |
|---|
| Poor red cell production |
| Anaemia of chronic disease and functional iron deficiency |
| Inflammation leading to functional iron deficiency |
| Reduced erythropoietin production because of acute kidney injury |
| Reduced erythropoietin production because of chronic kidney disease |
| Cancer-induced anorexia |
| Nutritional deficiencies of iron, folate, and vitamin $B_{12}$ |
| Bone marrow injury |
| Myelosuppressive chemotherapy/radiation treatment |
| Myelodysplastic syndromes |
| Others |
| Pure red cell aplasia |
| Bone marrow infiltration and inhibition of red cells production |
| IInduction of anti-erythropoietin (anti-EPO) antibodies after exogenous EPO use |
| Red cell destruction |
| Autoimmune haemolytic anaemia |
| Erythrophagocytosis |
| Microangiopathic processes |
| Hypersplenism |
| Red blood cells loss |
| Malignancy invading normal tissues causing blood loss |
| Tumor-related bleeding (gastrointestinal or uterine cancers) |

**Table 2.** Anaemia grading according to the National Cancer Institute

| Grade | Haemoglobin level/definition |
|---|---|
| 0 | ≥Lower limit of normal |
| 1 | 10 g/dl to lower limit of normal |
| 2 | 8.0–9.9 g/dl |
| 3 | 6.5–7.9 g/dl |
| 4 | <6.5 g/dl |
| 5 | Death |

The highest incidence of CRA in solid tumours is found in patients who have lung cancer, of which 70% will have anaemia. This is followed by 61% of patients with gynaecological malignancies. The frequency of anaemia also increases in patients with more advanced or poorly controlled cancer [2].

The interaction between the immune system, iron metabolism, and erythropoiesis has been considered to be a significant factor in the development of CRA. These interactions can be observed between several cytokines on different iron-homeostasis and erythrocyte-cell-production pathways. Inhibitory cytokines, such as tumour necrosis factor alpha (TNFα) and interleukin 1 (IL)-1, primarily work on the suppression of erythroid precursor cells and erythropoietin production [6,7]. The pathogenesis of functional iron deficiency, anaemia also includes the release of cytokines by the malignant cells itself. Tumour necrosis factor alpha, IL-1, and IL- 6 stimulate the synthesis of hepcidin in the liver [6,7]. The binding of hepcidin to ferroportin in the reticuloendothelial cells in the intestine interrupts stored iron or dietary iron from being utilized for the production of red blood cells. IL-1, IL-6, and hepcidin, cause the diversion of iron from erythropoiesis to the reticuloendothelial system [7,8]. Hence, functional iron deficiency is the result of iron blockage by multiple mechanisms, including decreased red cell survival, the suppression of renal EPO production, erythropoiesis inhibition, the sequestration of reticuloendothelial cells, and the inhibition of iron release by hepcidin [9].

## Cancer-related anaemia, symptoms, and quality of life

The symptoms of CRA can be present in patients with even mild anaemia but can vary according to the severity of the anaemia. The most common symptom is fatigue. Other symptoms of anaemia can also include headache, depression, nausea,

dizziness, loss of appetite, palpitations, dyspnoea, heart failure, and impaired cognitive ability.

Quality of life (QOL) can be severely affected. As a consequence, these symptoms can often impact the patient's daily activities of living and their ability to function optimally at home and in the workplace, as well as impact their activities of leisure and exercise capacity [2–4].

Various tools can be used to assess the severity of cancer-related fatigue secondary to anaemia. These tools help clinicians to understand the relation of the fatigue to the QOL of the patient. The Functional Assessment of Cancer Therapy – General or the Functional Assessment of Cancer Therapy – Fatigue is commonly used. Currently, there is no consensus concerning the preferred tool to use. Also, an evaluation of the mental state of the patient should preferably be conducted to ascertain if all symptoms are cancer related, or if symptoms are also because of a psychological element. Patients with cancer often suffer from depression as well. The Diagnostic Interview for Cancer-Related Fatigue Syndrome and a Structured Psychiatric Interview are psychological tools that can also be used to assist The Functional Assessment of Cancer Therapy – Fatigue (FAST-F) to obtain an accurate assessment. These could be tedious and impractical in clinical practice [10–12].

## Investigation of anaemia in patients with cancer

The primary goal in the treatment of CRA is to treat the underlying cause of the anaemia and to raise the haemoglobin to a level where symptoms can be relieved. The definitive treatment of CRA is the eradication of the underlying malignancy. However, this is not possible in many patients. A thorough evaluation of the patient must be made so that treatable causes can be excluded [2,13].

Proper evaluation of the patient should include a thorough history, physical examination, as well as serological examinations. Special investigations must be directed at the most likely cause and include a full blood count with a differential count and a reticulocyte count. Iron studies, C-reactive protein are necessary for ascertaining a cause, as well as making treatment decisions (Table 2). Nutritional anaemia's (iron, red cell folate, and vitamin B12 deficiencies) must also be included in the evaluation of an anaemic cancer patient. A bone marrow examination should be considered, as relevant factors such as relapsed disease or secondary malignancies in patients previously treated with chemotherapy are always a possibility. In malignancies associated with a high incidence of haemolysis, such as in chronic lymphocytic leukaemia, a Coombs test, lactate dehydrogenase, haptoglobin, and indirect bilirubin should be carried out. Endogenous erythropoietin levels may be determined in certain instances, such as in myelodysplasia to assess response to erythropoietin stimulating agents (ESAs). Guidelines are unclear which cut-off levels mandate treatment. It is important to review the history, examination, and blood findings together to make an accurate assessment of the cause of anaemia to implement the appropriate therapy. Reversible causes of anaemia should be actively sought out and addressed [2,13].

For those patients without an obvious reversible cause, treatment choices may involve blood transfusions, the use of ESAs, and iron supplementation in absolute or functional iron deficiency anaemia.

## Management in patients with cancer-related anaemia

Before ESAs were available, transfusion was one of the few therapies available, as well as androgen therapy. Androgen therapy is thought to increase the sensitivity of the erythroid progenitors to erythropoietin. In a very old study published in NEJM in the 1950s/1960s, an increase in erythropoietic activity was seen in women with breast cancer, who were given androgen therapy in the adjuvant setting. There were also studies done in the myelofibrosis setting. This is not standard practice as there is not much evidence to substantiate its use. Transfusion is the most successful way of raising the haemoglobin levels reasonably rapidly and, thus, relieving symptoms and improving QOL. The haemoglobin level is expected to rise by approximately 1 g/dl with each unit transfused. It is important to note that each unit of red blood cells also contains 200–250 mg of iron. Repeated transfusions carry the risk of iron overload, as the human body has no physiological mechanism to eliminate the excess iron accumulated by transfusion. Transfusions are indicated in patients that are symptomatic, and have a higher risk for poor tolerance of anaemia, such as age over 65 or patients with concomitant cardiovascular or respiratory disease. There are no clear recommendations at which level a patient should be transfused, but in general, mild asymptomatic anaemia or haemoglobin levels of more than 10 g/dl can be left untreated, or sometimes a cut-off level of 9 g/dl is used to start treatment [4,14▪▪].

Transfusions are associated with a number of complications, although now with better laboratory techniques and better donor screening, the risk of transmission of infections, namely human immunodeficiency virus and hepatitis B and C are

 

significantly less than before. Other complications include anaphylactic reactions, transfusion-related lung injury, transfusion-related circulatory overload, but these are usually more frequent following massive transfusions [4,15].

Many concerns have been raised concerning the safety of ESA treatment in terms of mortality, risk of venous thromboembolism and tumour progression. Some studies demonstrated a decrease in survival and increase in overall mortality [1,2,4,13].

The value of ESAs for the treatment of anaemia in cancer patients remains controversial. Clinical response associated with ESAs takes significantly longer than transfusion, and may take weeks to months to attain a response.

The main advantages of ESAs in the treatment of patients with cancer include, increase in haemoglobin levels and reduction in the requirement of blood transfusions and improvement in QOL. Additionally, ESAs may also improve cognitive function and cause a reduction in fatigue. Littlewood *et al*. have evaluated the response to EPO in patients with solid tumours and haematological malignancies. Cancer patients with anaemia, who were treated with nonplatinum-based chemotherapy, were registered in a multinational, double-blinded, randomized, placebo-controlled trial. Patients were prospectively stratified according to whether they had haematological malignancies or solid tumours. The mean rise in haemoglobin levels in patients with haematological malignancies was greater with EPO (2.2 g/dl) than with placebo treatment (0.3 g/dl). Treatment with EPO was associated with an improved QOL, whereas patients treated with placebo had a reduction in QOL. Vansteenkiste *et al*. obtained similar results in a double-blinded placebo-controlled randomized phase III trial with darbepoetin-α in patients with lung cancer. The group of patients who received darbepoetin required fewer transfusions (27%) compared with patients treated with placebo (52%) [16,17].

There have been many meta-analyses, which assessed risk versus benefit of ESAs. The improvement of QOL appears to be proportionate to the increase in haemoglobin of patients treated with an ESA. The ability of ESAs to reduce transfusion requirements was confirmed in a 2006 Cochrane review by Bohlius *et al*. The same meta-analysis showed that there was a trend toward an improvement in QOL in patients receiving ESA treatment [18].

Available ESAs are epoetins: epoetin-α, epoetin-β (Neorecormon), and darbepoetin-α (Aranesp). A pegylated formulation of EPO (methoxy PEG Epoetin-beta, Mircera, CERA) has been approved by the United States Food and Drug Administration (USFDA) in 2008 for use in the USA and was approved for use in Europe by the European Commission in 2007, and some biosimilars will be available in the future. Epoetin and darbepoetin have the same protein sequence but differ as they have different glycosylation patterns. Darbepoetin has a longer serum half-life. There seems to be no difference in safety and efficacy of different ESAs. In patients with solid tumours, the aim of treatment with ESAs is to reduce the need of red blood cell transfusions and complications, such as iron overload, transmission of infection, to improve QOL, and reduction in fatigue by improving the haemoglobin level of patients. ESAs can reduce the relative risk of receiving transfusions by 36%. Platinum-based chemotherapy regimens benefit more from treatment with ESAs. ESMO and ASCO guidelines recommend the use of ESAs in patients with haemoglobin levels of less than 10 g/dl on chemotherapy, to prevent a further decline and to increase levels by 2 g/dl. There is no indication for usage of ESAs in patients not being treated with chemotherapy. The National Comprehensive Cancer Network (NCCN) and the ESMO guidelines caution against the usage of ESAs in patients being treated with chemotherapy with curative intent. There is no clinical advantage in continuing ESAs in a patient who shows no clinical response within 6–8 weeks, as not all patients will benefit from the use of ESAs. ESAs should not be used in patients with a known hypersensitivity to ESAs or poorly controlled HT. Additionally, in patients where transfusions are contraindicated, for religious or personal reasons, ESA treatment is an alternative option, however, it should be pointed out that prophylactic use of ESA to prevent anaemia is not recommended by most guidelines [2,12,19,20].

The risks of thromboembolic events have been evaluated in a meta-analysis published by Bennett and colleagues in 2008. In total, 8172 patients from 38 phase III studies were assessed for the risk of thromboembolic events. The meta-analysis has demonstrated an increased risk of thromboembolic events, with a relative risk of 1.57 (95% CI: 1.31–1.87). It is important to point out that in this analysis, there was no statistically significant increase in the mortality rate when the study analysis was limited to patients receiving active treatment with chemotherapy or radiotherapy (hazard ratio: 1.09; 95% CI: 0.99–1.19) [21].

The risk of thromboembolic events should always be assessed in a patient who could potentially benefit from using an ESA. A very high-risk group where ESAs should be avoided is in patients with multiple myeloma using immunomodulatory agents. There are no data on the use of aspirin or

anticoagulants to prevent thromboembolic events with ESA use. Additional side-effects of ESAs include dyspnoea, urticarial rash, arthralgia, peripheral oedema, and injection site pain.

Two studies evaluated ESA therapy in breast cancer patients undergoing systemic chemotherapy. The Breast Cancer Erythropoetin Survival Trial (BEST) study and the PReoperative Erythropoeitin Paclitaxel ARansEp (PREPARE) study were both double-blinded, placebo-controlled phase III trials. Both trials showed a higher mortality rate in the patients where ESAs were used [22,23].

The Erythopoeitin in Head And Neck Cancer (ENHANCE) study and the Danish Head and Neck Study 10 (DAHANCA-10) study showed a reduction of time to locoregional progression in patients with head and neck cancer undergoing ESA treatment. In the ENHANCE study, the overall survival was reduced in patients treated with ESAs [24,25].

Three meta-analyses performed by Bennett, Bohlius, and Tonelli [20,26,27] reinforced that patients who have been treated with ESAs had a significant increase in mortality. Notably, these three meta-analyses included patients from studies where EPO was used off-label with target haemoglobin more than 12 g/dl. A separate meta-analysis conducted by Glaspy, noted that when analysing patients involved in trials where the haemoglobin target was less than12 g/dl, the overall mortality did not differ between patients undergoing ESA treatment or patients being treated with placebo [28].

The consideration to use ESAs must not be taken lightly as these agents are expensive. ESAs on one hand decrease the necessity for red blood cell transfusions but increase the risk for thromboembolic episodes and mortality because of tumour progression. Many studies suggest that ESAs improves QOL. However, it remains uncertain whether and how ESAs affect tumour control. The increase in cancer mortality and thromboembolic phenomena should be weighed against the potential advantages of ESA treatment, taking into consideration each patient's clinical features as well as patient's personal choice. Additional research is required to elucidate the cellular and molecular basis of the mechanisms of ESAs and their potential effects on cancer progression.

These safety concerns have urged the US Food and Drug Administration to develop the Risk Evaluation and Mitigation Strategies (REMS) for clinicians prescribing ESAs. REMS are a method to ensure safety and provide clinicians and patients with a suitable instrument to weigh the risks and benefits associated with the administration of ESAs. Currently, the NCCN guidelines recommend that clinicians who prescribe ESAs should do so using the REMS guidelines, with the patient's informed consent [14▪▪].

Under this program, providers who prescribe ESAs should counsel each patient on the risks and benefits of ESAs prior to each new course of ESA therapy commenced.

A functional iron deficiency is frequently observed in patients undergoing EPO treatment. An important point is the fact that iron studies, including serum iron, total iron binding capacity (TIBC), and serum ferritin, should be done before any form of anaemia treatment is considered, to rule out absolute iron deficiency (defined as a transferrin saturation <15% and a serum ferritin <30 ng/ml). This type of anaemia usually responds to oral or intravenous iron monotherapy without an ESA. The NCCN, ESMO, and EORTC [29] guidelines recommend that iron supplementation should be administered in patients to support adequate erythropoiesis in patients using ESAs. Iron levels should be monitored in these patients, as they often need supplemental iron. Iron deficiency secondary to cancer is usually defined by a transferrin saturation of less than 20%. Serum iron levels can be falsely elevated so caution must be taken when interpreting results. Clinical trials in cancer patients with anaemia receiving ESA together with oral iron, intravenous iron, or no iron at all revealed that patients taking an intravenous bolus had a higher increase in haemoglobin levels compared with patients receiving oral iron or no iron supplementation at all. [30–33]. In the study by Henry *et al.* [31] there was no statistical difference between those patients receiving oral iron or no iron supplementation. These responses highlight the importance of investigating possible iron deficiency as a cause of cancer-related anaemia. Additionally, intravenous iron administration is generally preferred over oral therapy because of abnormal iron metabolism and poor compliance when using oral therapy. NCCN recommends the use of supplemental iron in patients with a ferritin level less than30 ng/ml and transferrin saturation of less than 15%. Other guidelines are less specific. The use of iron therapy is usually in combination with an ESA, to optimise as well as decrease the duration of ESA usage [2,14▪▪,30–33].

## CONCLUSION

Anaemia is very prevalent in patients with malignant diseases and is associated with poor QOL. ESAs significantly increase haemoglobin levels, reduce transfusion requirements, and improve the QOL, by reducing fatigue in patients with CRA. Clinical trials and various meta-analyses demonstrated an

 

increased risk of thromboembolic events, shorter time to cancer progression, and a possible increased risk of mortality associated with the usage of ESAs. It has being shown that when ESAs are used according to current treatment guidelines and product label, they are useful and well tolerated agents for the treatment of anaemia in patients receiving radiotherapy and/or chemotherapy. Concurrent use of intravenous iron is associated with a better response to ESAs. Blood transfusions remain an efficient treatment in the management of anaemia in cancer patients, especially when there is a need for immediate increases in haemoglobin levels. In cancer patients receiving treatment with curative intention, the use of ESAs should be avoided. In the palliative setting, ESAs should be prescribed with caution and within the current guidelines.


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Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest


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