Journal of Experimental Pharmacology

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REVIEW

Experimental Drugs for Chemotherapy- and Cancer-Related Anemia

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Abstract: Anemia in cancer patients is a relevant condition complicating the course of the neoplastic disease. Overall, we distinguish the anemia which arises under chemotherapy as pure adverse event of the toxic effects of the drugs used, and the anemia induced by the tumour-associated inflammation, oxidative stress, and systemic metabolic changes, which can be worsened by the concomitant anticancer treatments. This more properly cancer-related anemia depends on several overlapping mechanism, including impaired erythropoiesis and functional iron deficiency, which make its treatment more difficult. Standard therapies approved and recommended for cancer anemia, as erythropoiesis-stimulating agents and intravenous iron administration, are limited to the treatment of chemotherapy-induced anemia, preferably in patients with advanced disease, in view of the still unclear effect of erythropoiesis-stimulating agents on tumour progression and survival. Outside the use of chemotherapy, there are no recommendations for the treatment of cancer-related anemia. For a more complete approach, it is fundamentally a careful evaluation of the type of anemia and iron homeostasis, markers of inflammation and changes in energy metabolism. In this way, anemia management in cancer patient would permit a tailored approach that could give major benefits. Experimental drugs targeting hepcidin and activin II receptor pathways are raising great expectations, and future clinical trials will confirm their role as remedies for cancer-related anemia. Recent evidence on the effect of integrated managements, including nutritional support, antioxidants and anti-inflammatory substances, for the treatment of cancer anemia are emerging. In this review article, we show standard, innovative, and experimental treatment used as remedy for anemia in cancer patients.

Keywords: hemoglobin, cancer-related anemia, chemotherapy-induced anemia, energy metabolism, inflammation, iron homeostasis, erythropoietin, interleukin-6

Introduction

Anemia in patients with cancer is still a relevant problem affecting both general health and quality of life. According to the definition of the World Health Organization, anemia occurs when hemoglobin (Hb) levels drop below 12 g/dL for women and 13 g/dL for men,[1] and severity ranges from mild to severe or life threatening. It can be classified into two important forms: (1) anemia occurring as an adverse event consequent to the toxic effect of anticancer treatment ("chemotherapy-induced anemia") and (2) anemia occurring as a manifestation of the disease itself, more aptly called "cancer-related anemia," resulting from systemic processes and immune system activation in cancer.[2] The incidence of anemia in patients with cancer depends on the tumor type and stage. Obviously, the incidence is particularly high in hematologic malignancies, affecting more than half of

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Received: 4 March 2021
Accepted: 21 April 2021
Published: 24 June 2021

patients at diagnosis; in these cases, anemia is caused by direct damage of the bone marrow and erythroid stem cells.[3] Among solid tumors, the most frequently associated with anemia are lung, gastrointestinal, and ovarian cancers.[3,4] Observational studies of large cohorts have reported low Hb levels in 20–30% of patients with cancer before starting any type of treatment and in 60–70% during anticancer therapy.[3,5] Indeed, chemotherapy can both induce new cases of anemia and unmask anemia induced by the tumor, explaining this substantial increase in rates. In patients not undergoing chemotherapy, the prevalence and severity of cancer-related anemia is correlated with the stage of disease, appearing in 60–80% of patients with advanced disease.[6] Considering the different mechanisms underlying anemia in patients with cancer, it is a nearly constant issue during disease progression.

Anemia has several deleterious effects in patients with cancer. The association between anemia and decreased survival in cancer is clearly established. Several observational studies have reported a negative impact of anemia on disease progression, response to chemo-/radiotherapy, survival, and risk of death, even for anemia occurring at an early cancer stage.[7–16] Although anemia may be a consequence of more aggressive forms of cancer, which have worse outcomes, the additional mechanisms unrelated to the tumor may affect prognosis in patients with anemia. For example, anemia could increase hypoxia in the tumor microenvironment, a condition that is associated with resistance to radiotherapy and chemotherapy, tumor growth, tissue invasion, metastasis, poor outcomes.[17] The anemic state, in proportion to its severity, leads to a set of symptoms, such as dyspnea, fatigue, dizziness, anorexia, lack of concentration, and depressed mood, and these symptoms compromise performance, daily functionality, and quality of life (QoL).[18–20] As an additional consequence, adherence to anticancer treatments can be compromised by the reduced performance status due to anemia. Collectively, these factors make anemia a clinically relevant condition in patients with cancer, emphasizing the importance of investigations and management. In the present review, we describe the types of anemia in patients with cancer, their understanding mechanisms, and therapeutic strategies, including conventional treatments as well as novel and experimental approaches targeting iron metabolism, erythropoiesis, nutrient deficiencies, and inflammation. Literature search was performed by PUBMED using the following key words cancer-related anemia, chemotherapy-related anemia, iron AND cancer, Erythropoiesis AND cancer, Erythropoietin AND cancer, epoetin AND cancer, hepcidin AND cancer, functional-iron deficiency AND cancer, hemoglobin AND cancer, blood transfusion AND cancer, anemia AND treatment AND cancer. As for treatment we included "Clinical Trial" [Publication Type] OR "Randomized Controlled Trial" [Publication Type] OR "Clinical Trial, Phase III" [Publication Type] OR "Clinical Trial, Phase IV" [Publication Type] OR "Meta-Analysis" [Publication Type] OR "Practice Guideline" [Publication Type].

Types of Anemia in Patients with Cancer

Anemia in patients with cancer can have various, non-mutually exclusive underlying causes. As in all forms of anemia, the etiopathogenetic mechanisms underlying low hemoglobin levels in patients with neoplasms include defective red blood cell production (impaired erythropoiesis) and increased destruction (hemolysis) or blood loss.[21] These mechanisms can be induced directly by cancer, as observed in cases of tumor infiltration of the bone marrow, neoplasms leading to bleeding, or chronic inflammation-related cancers, or can be induced by cancer treatments. In the latter case, anemia related to chemotherapy is the most representative form of drug-induced anemia. Notably, anticancer treatments have different associations with anemia depending on the setting. Pure chemotherapy-induced anemia occurs as an adverse event during anticancer treatments in the adjuvant setting; thus, it appears in patients who were not previously anemic and are in good general health. When chemotherapy is used as the principal treatment in neoadjuvant setting or for advanced or inoperable malignancies, a systemic disease induced by cancer is present, and chemotherapy can unmask latent anemia or aggravate pre-existing anemia. Thus, in patients with advanced cancer, the effects of anticancer treatments on erythropoiesis may largely overlap with cancer-related chronic inflammation and subsequent cancer-related anemia.

It is important to consider the type of anemia because treatment responses may differ, particularly since cancer-related anemia is related to a more complex set of pathogenetic mechanisms linked to the state of chronic inflammation (Figure 1). These mechanisms must be understood to improve the management of patients with cancer-related anemia.

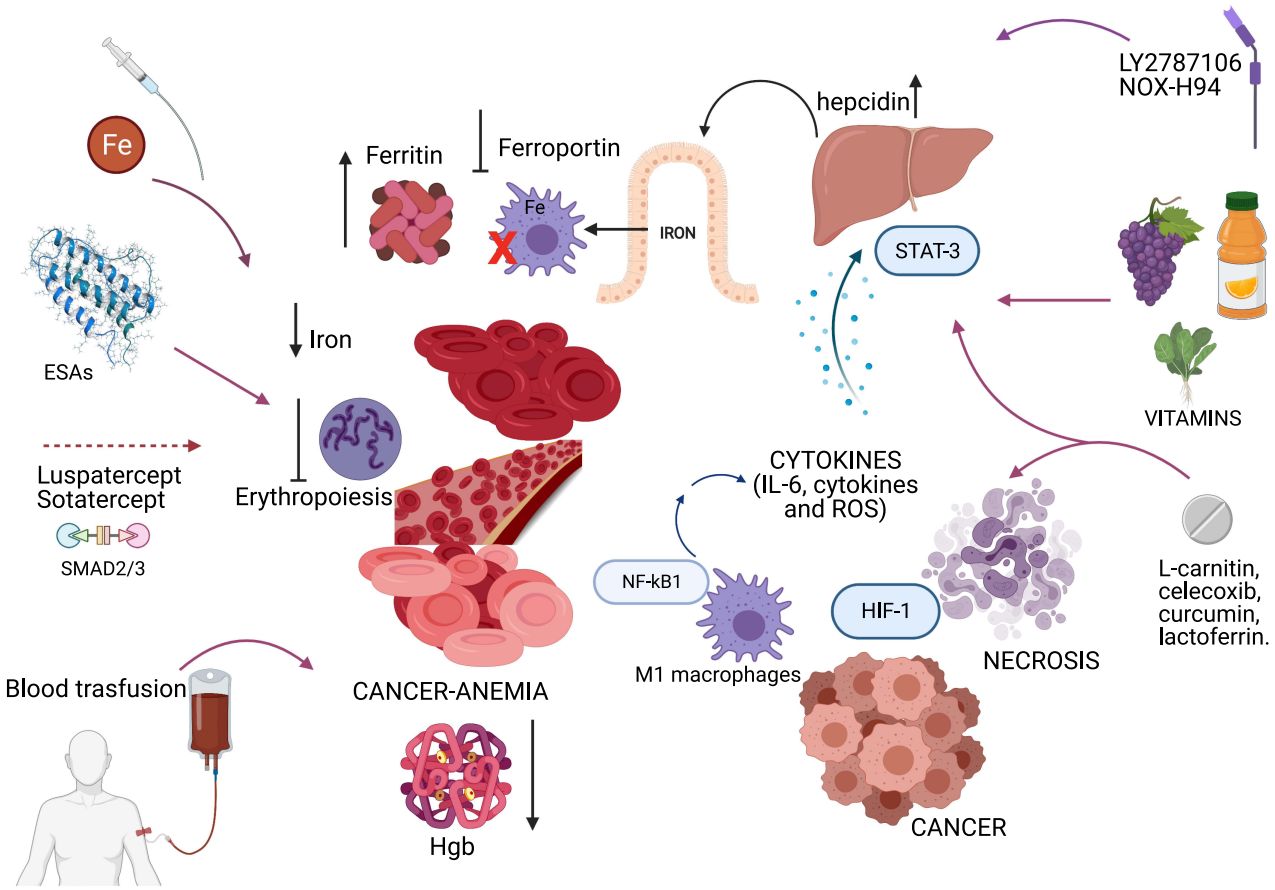

Figure 1 Pathogenetic mechanisms of cancer-related anemia and main related targeted approaches. The pathogenesis of cancer-related anemia involves multiple mechanisms induced by chronic inflammation associated to cancer and leading to functional iron deficiency and impaired erythropoiesis. Then, a multitargeted approach including conventional treatment such as ESAs, blood transfusion, iron therapy, as well as drugs targeting the inflammatory pathway, modulators of the iron metabolism, hepcidin antagonists, novel regulators of erythropoiesis and nutritional support should be considered. Figure was created in BioRender.com.

Abbreviations: ESAs, erythropoiesis stimulating agents; Hgb, haemoglobin; HIF, hypoxia inducible factor; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; IL, Interleukin; ROS, reactive oxygen species; STAT-3, signal transducer and activator of transcription 3.

Cancer-Related Anemia

Clinically, cancer-related anemia is usually normochromic and normocytic, with a low reticulocyte count.[22,23] Moreover, it is characterized in most most patients by low levels of EPO.[24] Iron blood concentrations can be within normal values, despite an iron deficiency in 30–60% of patients with cancer.[25] Usually, the total iron binding capacity is reduced, and ferritin blood values are elevated.[26] As with various chronic diseases, cancer-related anemia is associated with chronic inflammation. Even if tumor cells themselves produce cytokines, cancer at an advanced stage and tissue necrosis induce the activation of immune cells (mainly macrophages) and the subsequent secretion of proinflammatory cytokines, such as interleukins (IL-6, IL-1, etc.), tumor necrosis factor alpha (TNF-α), interferon gamma (IFN-γ) and amount of various chemokines.[22] Increases in systemic inflammation finally lead to anemia via several overlapping mechanisms: a negative impact on erythroid precursors in the bone marrow with inadequate erythropoiesis, reduced production of erythropoietin (EPO), shortened red blood cell survival, and impaired iron metabolism in the reticuloendothelial system.[2,22,27,28] Mainly, the negative effect on erythropoiesis is subsequent to iron restriction, a direct inhibitory effect on erythroid precursors, and a possible reduction in cytokine-induced EPO synthesis.[23,28] Furthermore, some cytokines can indirectly reduce the expression of hypoxia-inducible factor 1 (HIF1),[23] a transcription factor induced by hypoxia that stimulates EPO synthesis in the kidney.[29] As clinical evidence for inadequate erythropoiesis, in cases of cancer-related anemia, responses to EPO treatment may be insufficient.[24] The shortened erythrocyte survival can be attributed to the activation of macrophages by cytokines, which may increase red blood cell destruction. Moreover,

increased erythrocyte fragility could follow increased oxidative stress[30] in patients with advanced cancer because of increased production of reactive oxygen species (ROS) under chronic inflammation.[31,32] With respect to impaired iron metabolism, IL-6 and hepcidin have central roles. IL-6, produced both by cancer cells and M1 polarized macrophages, is a potent stimulator of hepatic hepcidin synthesis and hepcidin, in turn, is a modulator of iron metabolism by acting as an inhibitor of ferroportin, which allows trans-membrane iron transport.[33] Increased hepcidin levels limit the intestinal absorption or iron and prevent iron release from macrophages and reticuloendothelial cells.[33] This creates a "functional" iron deficiency (FID), even if iron stores are appropriate. As proof of the link between inflammation, iron metabolism, and anemia, patients with solid tumors at different sites and stages show an inverse correlation between hemoglobin levels and IL-6, hepcidin, inflammatory markers (fibrinogen, C-reactive protein, and ferritin), and ROS, and IL-6 is an independent predictor of the hemoglobin concentration.[31] In the same study, hemoglobin levels were positively correlated with leptin, cholesterol, albumin, and body mass index, which are generally related to nutritional status. Indeed, cancer-related anemia in the advanced stage of disease can be affected by the nutritional status of patients due to reduced iron and vitamin intake. In fact, cancer-related anemia is frequently associated with weight loss, anorexia, and cachexia.[2,34]

Obviously, in patients with systemic neoplastic disease, the initiation of anticancer therapies can worsen or unmask the state of cancer-related anemia, and the two mechanisms underlying anemia (ie, the mechanisms linked to chronic inflammation and linked to chemotherapy) overlap. Conversely, if chemotherapy is effective and induces a regression of tumor cells, levels of inflammation should be reduced, thereby attenuating cancer-related anemia. From this perspective, effective chemotherapy, with adequate nutritional and symptomatic support, is curative of the systemic manifestations of cancer and could effectively resolve cancer-related anemia. Clinical studies are required to investigate trends in anemia according to the response to chemotherapy.

Factors Involved in Chemotherapy-Induced Anemia

Chemotherapy-induced anemia is hypoproliferative due to the toxic effect of anticancer treatments on bone marrow or to a nephrotoxic effect, influencing EPO production (Figure 2). The severity of chemotherapy-induced anemia is conventionally defined by the Common Terminology Criteria for Adverse Events (CTCAE) proposed by the National Cancer Institute (NCI), which describes five grades of severity for each adverse event caused by cancer therapies.[35] According to this system, chemotherapy-induced anemia is classified as mild (grade 1 toxicity) for hemoglobin levels below the normal range to 10 g/dL; moderate (grade 2 toxicity) for hemoglobin levels between 8.0 and 10.0 g/dL; severe (grade 3 toxicity) for hemoglobin levels between 6.5 and 7.9 g/dL; life-threatening (grade 4 toxicity) when it is below 6.5 g/dL; and deadly (grade 5 toxicity). The incidence and severity of chemotherapy-induced anemia of course depend on the type of drug, dose, intensity, and number of cycles. In a multicenter study of more than 2800 patients with solid tumors, the incidence of anemia rose from 17% before the first chemotherapy cycle to 35% at the sixth cycle; patients with ovarian and lung cancer showed the highest prevalence of chemotherapy-induced anemia.[36] Grade 3–4 anemia was found during chemotherapy in 5.5% of cases overall in a series of Chinese patients with solid tumors who were not anemic before the start of treatment.[37] Factors associated with an increased incidence and severity of anemia are advanced age and concomitant leukopenia and thrombocytopenia.[37] All anticancer treatments may result in anemia; however, the condition is often induced by platinum-based regimens.[37,38] Indeed, beyond the direct toxic effect on erythropoiesis, platinum-based chemotherapy may cause nephrotoxicity with a subsequent drop in EPO production.[39] Moreover, cisplatin increases ROS production and ROS in the kidney inhibits EPO synthesis, probably acting as negative regulator of EPO gene transcription.[40,41] It is conceivable that combination chemotherapy further increases the risk of anemia.[38] Hematotoxicity and anemia are also observed during anticancer treatment with targeted therapies, both in combination with conventional chemotherapy and alone.[42] Generally, these agents cause low-grade anemia (grade 1–2); however, the mechanisms underlying their effects not well-established.[42] PARP inhibitors are a new class of anticancer drugs recently developed for the treatment of ovarian, pancreatic and breast cancer. They may induce hematologic toxicity, potentially affecting all blood cell lines. In a meta-analysis of the adverse effects of olaparib from Phase II–III studies, 32% of patients with advanced ovarian cancer had all-grade anemia and 13% had grade 3–4 anemia.[43] Hematologic toxicity leads to the discontinuation of niraparib treatment in almost 15% of patients.[44] The exact mechanism by which PARP inhibitors confer

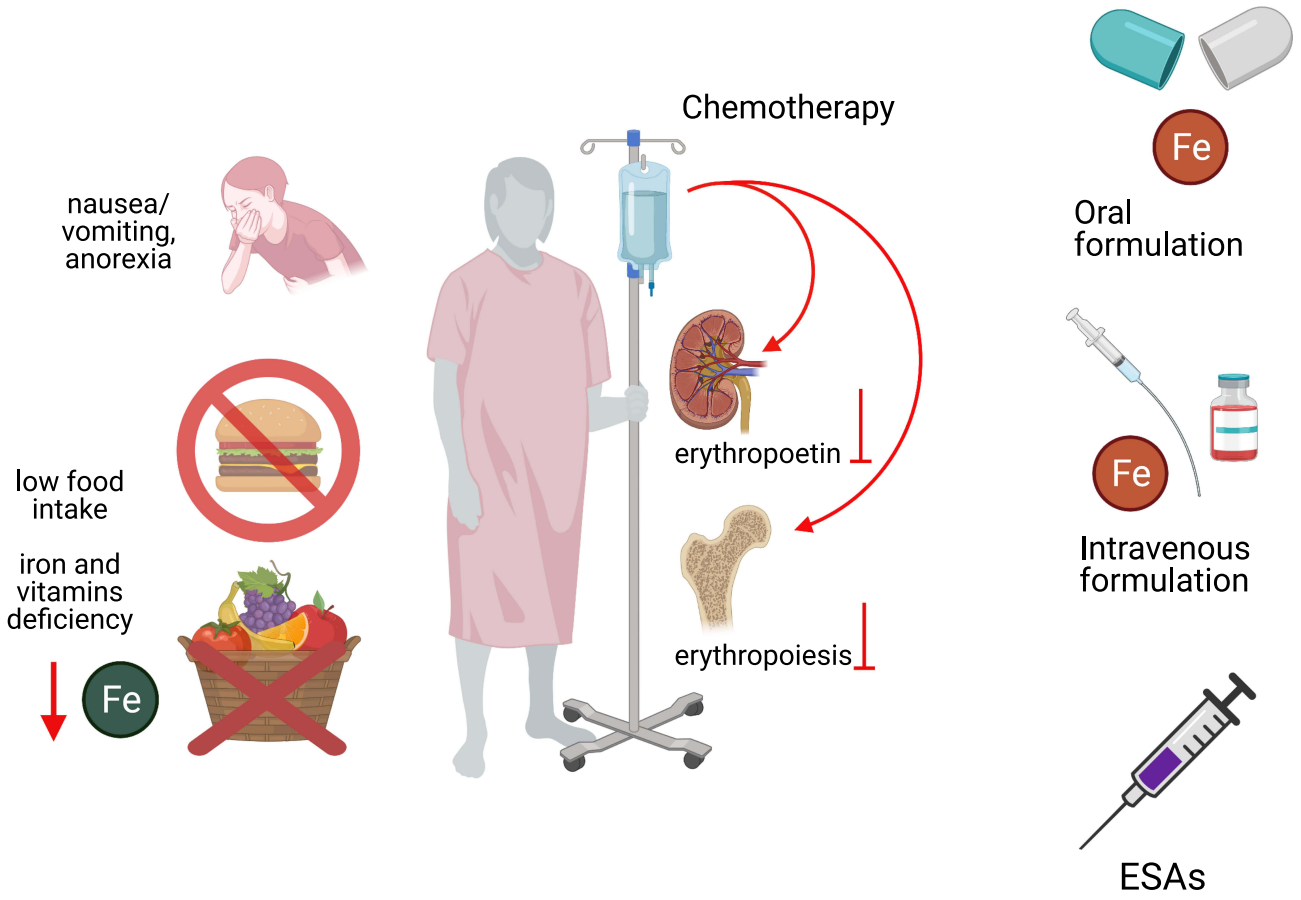

Figure 2 Pathogenesis of chemotherapy-induced anemia and therapeutic strategies. Chemotherapy-induced anemia is related to the toxic effect of anticancer treatments on bone marrow or to a nephrotoxic effect, which negatively influence EPO production. Additionally, anticancer treatments can induce gastro-enteric side effects, such as anorexia, nausea, and vomiting, and diarrhoea, which lead to iron and vitamins deficiency. Thus, treatment includes ESAs, iron therapy (oral or intravenous iron) and nutritional support. Figure was created in BioRender.com.
Abbreviations: Fe, iron; ESAs, erythropoiesis stimulating agents.

hematologic toxicity in humans is unknown. It may be related to genomic instability induced by these drugs; however, other molecular pathways could be involved, including oxidoreductive reactions and oxidative stress accumulation. PARP inhibitors approved for cancer therapy are not selective for different PARP isoforms. However, emerging evidence suggests that various PARP proteins govern different functions.[45] For example, in mice, PARP-2 (and not PARP-1) is fundamental for the survival of erythroid precursors and hematopoiesis.[46,47] Notably, PARP-2-deficient mice develop chronic anemia with low red blood cell counts, consequent to replicative stress in erythroid precursors, resulting in arrest in phase G2/M of the cell cycle.[47] Instead, PARP-1 is involved in the regulation of iron metabolism via the inhibition of *HFE* gene expression, which finally controls hepcidin synthesis.[48]

Chemotherapy can contribute to anemia via other mechanisms, beyond hematotoxicity. Indeed, anticancer treatments can induce gastro-enteric side effects, such as anorexia, nausea, and vomiting, and diarrhea (Figure 2). These side effects objectively decrease food intake or lead to a loss of nutrients, vitamins, and minerals, ultimately affecting erythropoiesis.[26,49]

In particular, we can affirm that chemotherapy-induced anemia can occur as pure adverse event in patients with early-stage cancer who were not anemic before starting chemotherapy. In this context, the gold standard treatment is erythropoiesis-stimulating agents (ESAs), which restore the stimulation of the bone marrow and erythroid precursors (Figure 2). If, instead, there is an underlying condition induced by advanced cancer, chemotherapy-induced anemia and cancer-related anemia overlap, and management should involve a multimodal approach accounting for the

severity of anemia, the associated inflammatory state, the impairment in iron metabolism, and the nutritional status (Figure 1).

Therapeutic Approaches for Anemia in Patients with Cancer

The optimal treatment strategy for anemia depends on the exact underlying etiopathogenetic mechanisms, which, particularly in cancer-related anemia, generally involve IL-6-related inflammation with associated FID, oxidoreductive stress, and nutritional disorders. The careful characterization of anemia and associated clinical parameters is essential to establish management strategies, and other potentially remediable comorbidities should be identified and corrected. The initial evaluation of anemia in patients with cancer involves observations of signs and symptoms, exhaustive evaluations of blood counts, red blood cells, hemoglobin values, hematocrit and reticulocyte counts, and examinations of the nutritional status and potential deficiencies (based on iron stores, folates, and vitamin B12), such as deficiencies in renal function and endocrine function, to exclude comorbidities linked to anemia.[26] It is critical to look for signs of chronic inflammation, such as high C-reactive prot ein (CRP), fibrinogen, and serum ferritin levels and low transferrin saturation.[31,50,51] Evaluations of parameters related to iron metabolism (serum iron, ferritin, transferrin saturation percentage, and hepcidin, if possible) permits the detection of an iron deficiency (ID) or FID.[52] Finally, the Glasgow Prognostic Score (GPS), obtained by the ratio between inflammation (CRP) and nutritional status (albumin), is of great value to clinicians, as it reflects the systemic inflammatory-nutritional status of patients[53] and is correlated with the severity of anemia.[31]

Treatments for anemia in patients with cancer aim to restore hemoglobin concentrations and red blood cell counts and thus to optimize blood and tissue oxygenation, resulting in improvements in energy and fatigue. Increased hemoglobin levels improve anemia-related symptoms and QoL, with the best benefits obtained for values of ≥12 g/dL.[54] To ensure adequate erythropoiesis, the rebalancing of iron metabolism is essential. An iron deficiency, regardless of anemia, could itself contribute to fatigue.[55] Importantly, iron homeostasis involves all hemoproteins, and these do not participate exclusively in oxygen transport and storage (hemoglobin and myoglobin) but also contribute to many fundamental metabolic pathways, such as energy production, protection from oxidative damage, and the regulation of inflammation. Cytochromes, catalases, peroxidases, and cyclooxygenase are just a few examples of hemoproteins.[56]

Therefore, we believe that an effective approach to cancer anemia must make use of multimodal interventions that include drugs and nutraceuticals capable of attenuating these conditions in a tailored manner. Conventional treatments available for anemia in cancer include ESAs, blood transfusions, and iron therapy. However, combined approaches including modulators of iron metabolism, nutritional support, or anti-inflammatory drugs should be considered.[2,57]

Red Blood Cell Transfusions

Owing to the capacity to rapidly restore hemoglobin levels and tissue oxygenation, red blood cell transfusion remains the preferred treatment for patients with symptomatic severe anemia. It has been estimated that the infusion of 1 unit of concentrated erythrocytes is able to increase hemoglobin levels by 1 g/dL and the hematocrit by approximately 3%.[58] Thus, red blood cell transfusion confers rapid improvements in well-being and related QoL.[59] However, it is more difficult in patients with cancer than in the general population to define the hemoglobin threshold under which transfusion therapy should be employed, and guidelines for red blood cell transfusions fail to provide specific recommendations in this setting.[60] Generally, transfusions are recommended to restore severe anemia and obtain hemoglobin levels above 7–8 g/dL, with the minimum number of red blood cell units required.[61] However, more recent guidelines agree that the use of erythrocyte transfusion should depend mainly on symptomatology, the rate of the hemoglobin decline, and individual risk factors, such as comorbidities and concomitant conditions.[31,62,63] The presence of bleeding, ischemic diseases, the need for surgery, or the start of chemotherapy, for example, can prompt the choice of transfusion, even when hemoglobin values are above 8 g/dL.

There are some concerns regarding transfusion therapy. There is an intrinsic risk of acute adverse reactions and infection transmission. The introduction of several modern safety systems for blood supplies has considerably reduced the risk of infections, and particularly the risk of viral infections.[64] However, the risks of hemolytic and allergic reactions, alloimmunization, iron and circulatory overload, and possible immunosuppression are not negligible.[65] There is evidence for an increased risk of thromboembolic

events in patients with cancer undergoing blood transfusions with an associated increased risk of mortality.[66] There is a well-known thrombotic risk associated with cancer, especially in advanced-stages. Prophylactic anticoagulant use should reduce this risk, and studies are required to evaluate if routine low-molecular-weight heparin reduces the thrombotic risk and related mortality.

Notably, a relationship between the peri-operative need for erythrocyte transfusion and negative oncological outcomes has been reported for several types of cancer. Although the mechanisms underlying poor outcomes have yet to be determined, it is possible that the immunosuppressive effect of blood transfusions is involved.[67–69] For these reasons, transfusion must be reserved for cases of severe symptomatic anemia and specific associated comorbidities.

Erythropoiesis-Stimulating Agents

Several randomized clinical trials and meta-analyses of cancer patients receiving chemotherapy have demonstrated the better efficacy of ESAs than the placebo in increasing hemoglobin levels and reducing erythrocyte transfusions.[70–73] Among them, a Cochrane meta analysis published in 2012 on the efficacy of ESAs in patients with cancer, involving 91 trials with more than 20,000 participants, showed an overall significantly greater hematological response in subjects using ESAs versus controls (risk ratio 3.39, 95% confidence interval (CI): 3.10–3.71) and a significant decrease in red blood cell transfusions (risk ratio 0.65, 95% CI: 0.62–0.68).[73] The same meta-analysis also highlighted improvements in QoL, fatigue, and other anemia-related symptoms in patients receiving ESAs, according to the increase in hemoglobin concentrations.[73] Although some trials have shown conflicting results concerning the changes in QoL in patients with cancer receiving ESAs, a recent systematic review concluded that ESAs are associated with a clinically important improvement in anemia-related symptoms.[74] Thus, the effectiveness of ESAs for the treatment of chemotherapy-induced anemia is well supported.

ESAs act by stimulating the production of red blood cells in the bone marrow, leading to an increase in hemoglobin values obtainable in a few weeks. The therapeutic goal is the achievement and maintenance of hemoglobin values not requiring blood transfusions.

ESAs include recombinant human EPO (rHuEPO), and these have been approved for the treatment of anemia in cancer since the early 1990s. Epoetin-α, epoetin-β, and darbepoetin-α, modified recombinant EPOs, are also available for clinical use.[75] These agents show similar effectiveness in clinical studies but have some pharmacokinetic differences. Darbepoetin-α boasts a longer half-life, which allows it to be administered every 2 or 3 weeks, although the time to achieve desired hemoglobin values may be longer than those for epoetin; agents with a shorter half-life require weekly administration.[75,76] Original rHuEPO drugs are expensive, which has limited their use in many contexts. Biosimilar drugs share the same physical-chemical and biological properties and pharmaceutical form as the original drug and have demonstrated similar efficacy and safety in clinical trials, with reduced costs.[77] Indeed, data available from studies on biosimilar epoetins were sufficient for their approval (both by the Food and Drug Administration-FDA- and European Medicines Agency-EMA) for clinical use with the same indications of original rHuEPOs.[26,78,79]

Of note, most clinical studies of ESAs efficacy have focused on subjects undergoing chemotherapy, irrespective of the treatment setting (adjuvant, induction chemotherapy with curative intent, or palliative). Thus, there is no clear evidence for the effectiveness of ESAs on different forms of anemia in patients with cancer. In cancer-related anemia without anticancer treatments, some studies have demonstrated significant increases in hemoglobin concentrations and hematologic responses after treatment with darbepoetin-α in comparison with those for placebo treatment.[80,81] The incidence of transfusions in the treated arms was lower than that in untreated arms, although the difference was not significant.[80,81] In a Cochrane meta-analysis, Tonia et al divided cases into subgroups based on the treatment type and found that patients with cancer and anemia not receiving chemotherapy benefit from ESAs administration, showing a positive hematologic response and changes in hemoglobin levels as well as a significant reduction in red blood cell transfusions.[73] However, when target hemoglobin concentrations exceeded 12 g/dL, negative effects emerged, such as thrombotic events or improper disease progression.[73,82–84] It could also be hypothesized that anemia is a symptom of the tolerance phase of the interaction between the tumor and host and acts as a defense mechanism in the final stages of the disease. It follows that anemia treatment would remove this defense and would attenuate cancer cell viability. However, this hypothesis has never been evaluated. The increase in thrombotic risk observed during ESAs treatment can be explained by the increased hematocrit

percentages.[73,82–86] Thus, it is necessary to evaluate other individual risk factors before starting ESAs. The risk of ESAs treatment appears to be lower when initial hemoglobin values are below 10 g/dL; however, additional evidence is needed to support this conclusion.[82] In a recent meta-analysis evaluating risks of ESAs in patients with cancer including only randomized controlled trials in which treatment was started when hemoglobin concentrations were <11 g/dL and the target values were no more than 13 g/dL, thromboembolic events did not differ between ESAs treatment groups and controls.[85] However, these data was not confirmed by previous meta-analyses. Owing to the lack of prospective randomized trials evaluating the role of antithrombotic therapy during ESAs use, actual guidelines do not recommend the default use of anti-coagulant prophylaxis to prevent thromboembolic events in patients with cancer undergoing ESAs treatment.[26,63,87] Nevertheless, since oncological subjects present an intrinsic pro-coagulant risk and chemotherapy can increase this risk,[88] consistent thrombotic prophylaxis should be considered, especially when ESAs are used. Regarding neoplastic progression during ESAs, it has been suggested that these agents directly may stimulate tumor cell growth. Some evidence from in vitro studies supports this hypothesis.[89,90] However, these effects have not been confirmed in vivo. Notably, recent clinical studies have confirmed that ESAs do not have an impact on oncological outcomes if given according to the label.[91–94] Of note, the effects of various doses and overall ESAs exposure on patient outcomes remain open questions. Other potentially severe adverse events linked to ESAs include hypertensive events; accordingly, ESAs should be avoided in patients with uncontrolled hypertension and blood pressure values should be evaluated during treatment. Rare cases of thrombocytopenia and pure red cell aplasia have been reported.[26,73,95]

Considering these findings, the FDA restricted indications of ESAs to patients with cancer and anemia during chemotherapy with palliative intent, urging caution regarding the possibility of disease progression.[62,63] Treatment might be started when hemoglobin levels are below 10 g/dL, with the aim to reach 12 g/dL and avoid red blood cell transfusions. Such warning has been shared by the guidelines published on this topic by the main International Societies (ASCO/ASH and NCCN), which indicate that ESAs are not recommended in patients with cancer not receiving myelosuppressive therapies.[26,62,63,96] During ESAs treatment, hemoglobin values should be monitored every 1–2 weeks to evaluate the response. Dose reductions should be considered if hemoglobin levels increase by 1 g/dL; a dose escalation is justified if there is no response (ie, Hb increase less than 1 g/dl and Hb below 10 g/dl) in 4 or 6 weeks of epoetin or darbepoetin, respectively.[26,62] If no hematologic effects emerge after 8 weeks, treatment should be stopped.[26,62]

Iron Therapy

The choice to include iron therapy in the management of patients with cancer and anemia must necessarily be guided by the evaluation of the iron status. Indeed, as already mentioned, anemia can be associated with an absolute ID, characterized by a depletion of the total body iron stores, or FID consequent to iron sequestration from the reticuloendothelial system, induced by chronic inflammation mechanisms and IL-6 via hepcidin pathways. Of course, iron supplements are required if ID is present, while new approaches that mobilize sequestered iron may be more suitable in FID.

ID is present in 30–60% of patients with cancer.[25] When ID is present and no conditions impair enteric absorption, both oral and intravenous (IV) iron are efficient and recommended treatments.[26] The majority of studies of the efficacy of iron treatment in the setting of chemotherapy-induced anemia have used IV administration. However, some factors may favor the use of oral iron, which is less expensive and more practical for home therapy. In cases with no FID and therefore with a deficiency not associated with inflammation, oral therapy may be used for the treatment of chemotherapy-induced anemia with associated ID. The choice of the administration route should depend on the onset and grade of ID and anemia as well as the likelihood of gastrointestinal absorption.[53] Oral iron is administered as iron salts or iron carbohydrates, and the bivalent ferrous form shows better bioavailability. However, oral iron may have many limitations in cancer patients such as the compliance given it is required for several months to be effective as well as the poor tolerance and side effects including mainly nausea, vomiting, constipation, abdominal pain, and GI upset in a significant proportion of patients.[97]

Intravenous iron includes carbohydrate formulations, such as ferric gluconate, ferric sucrose, or low-molecular-weight iron dextran, and glycan-coated drugs, such as ferric carboxymaltose, ferric isomaltoside, and iron ferumoxytol.[26,98] Carbohydrate ferric formulations require repeated administrations at low doses, while glycan-coated

formulations, which are grouped as third generation IV iron compounds, can be infused at a single time at high doses.[99] Common adverse events for IV preparations include dyspnea, hypo-/hypertension, headache, dizziness, and allergic reactions (observed mainly with iron dextran).[98,100] Notably, the third generation IV iron formulations are proven to be safer with very rare side effects with high advantages in terms of improving compliance and tolerance, and bypassing the hepcidin-ferroportin pathway that controls iron absorption.[97] These latter formulations do not require test dose to prevent/predict allergic reaction; however, they need to be given in a facility with resuscitation capabilities and with trained staff on managing anaphylaxis in case of rare reactions.[97]

Several clinical trials have evaluated the addition of IV iron to ESAs therapy versus ESAs alone for the treatment of chemotherapy-induced anemia. These trials have demonstrated synergistic effects of ESAs and IV iron. Iron strengthens the hematological response to ESAs by improving hemoglobin levels and times to achieve these levels and by reducing ESAs doses and red blood cells transfusions.[53,101–104] Thus, the combination of ESAs and IV iron therapy is recommended in cancer patients with anemia undergoing chemotherapy with concomitant ID.[26,63,96]

Currently, the role of iron supplementation in patients with cancer-related anemia is more controversial. In this setting, FID can be present, where body iron is not available for erythropoiesis and is retained in the reticuloendothelial system. It is important to remember that FID is associated with limited gastrointestinal absorption; thus, oral iron is not applicable. In some cases, IV iron administration could force metabolic defects and partially support erythropoiesis. The best effects in terms of the hemoglobin response for IV iron plus ESAs or IV iron alone in patients with chemotherapy-induced anemia and FID have been observed when hepcidin concentrations are relatively low.[105–107] Thus, hepcidin levels are a good predictor of the response to IV iron administration in patients with cancer and anemia with a high probability of FID. If hepcidin dosing is not available, analyses of the iron status (serum ferritin, transferrin saturation percentage) and inflammatory markers to detect absolute ID or FID can guide the use of iron therapy. As reported, in the case of FID, iron administration may not have the desired effects on the underlying, inflammation-induced alteration in iron metabolism. Furthermore, an iron overload can have harmful effects by increasing ROS production and oxidative stress, which can lead to mitochondrial and cellular damage.[108] Novel approaches based on the mobilization of iron from the reticuloendothelial system and the antagonism of hepcidin function are under investigation and are expected to play an important role in the treatment of FID and cancer-related anemia.

Experimental Drugs Targeting Iron Metabolism

Lactoferrin

As innovative modulator of iron metabolism, lactoferrin, an iron-binding protein belonging to the transferrin family with antibacterial, antioxidant, and immunomodulatory properties, has yielded interesting results with respect to the treatment of cancer-related anemia.[109] In a randomized clinical trial of patients with cancer-related anemia starting chemotherapy, we compared the efficacy of rHuEPO combined with IV iron or oral lactoferrin for the treatment of anemia.[110] In both arms, hemoglobin concentrations increased significantly; however, as added value, patients treated with lactoferrin exhibited a reduction in ferritin levels while the iron arm showed increased levels. These data confirm that lactoferrin functions as modulator of iron metabolism and is therefore useful for the management of anemia associated with iron dysregulation. Moreover, patients with cancer could benefit from the antioxidant and immunomodulatory effects of lactoferrin, and further studies on this topic are needed.

Hepcidin Antagonists

As described above, IL-6 and hepcidin contribute to alterations in iron metabolism in states of chronic inflammation. Experimental drugs under investigation for the treatment of anemia associated with iron dysregulation generally aim to reduce hepcidin production, to neutralize its biological effect, or to inhibit its action on ferroportin.[98] These drugs are also promising in combination with ESAs, which increase the availability of endogenous iron and enhance erythropoiesis. Among hepcidin antagonists, two promising drugs that act as hepcidin-neutralizing agents are now under evaluation in clinical trials. A neutralizing monoclonal anti-hepcidin antibody, LY2787106, stimulates erythropoiesis and modulates serum iron in animal models of inflammation-induced anemia.[111] A phase-I study of the pharmacokinetics, safety and efficacy of this compound in cases of anemia with non-myeloid advanced cancer and high hepcidin concentrations showed that LY2787106 was well-tolerated and induced dose-dependent increases in

serum iron and transferrin saturation.[112] A second hepcidin antagonist, NOX-H94 or lexaptepid, is a structured mirror-image L-enantiomeric oligonucleotide created to bind to and inhibit hepcidin.[113] In a phase-IIa study of patients with cancer and anemia, this drug increased hemoglobin levels in 5 of 12 participants and reduced ferritin concentrations.[114]

Prolyl Hydroxylase Inhibitors

Another experimental class of drugs is prolyl hydroxylase inhibitors, which protect HIFs from degradation and, consequently, increase tissue concentrations. HIFs are transcription factors that act in conditions of low tissue oxygenation, mediating the cellular response to hypoxia. In the kidney, HIF-2α directly promotes EPO synthesis. HIFs can also promote iron release from enterocytes and macrophages, respectively, via the increased transcription of ferroportin and hemeoxygenase-1 (involved in iron recovery from macrophages hemoglobin degradation).[115] Several prolyl hydroxylase inhibitors have been tested in phase-II and phase-III trials as orally active drugs, mainly for the treatment of anemia induced by chronic kidney disease.[116,117] To date, no studies have evaluated the effects of this pharmacological class on anemia in patients with cancer owing to possible effects on tumor growth. Indeed, HIF stimulates angiogenesis via the transcription of pro-angiogenetic factors, such as vascular endothelial-growth factor (VEGF). In a mouse model of VEGF-sensitive breast cancer, a prolyl hydroxylase inhibitor had no effect on tumor development or progression.[118] Further studies of the oncologic safety of prolyl hydroxylase inhibitors are required before they are tested in patients with cancer.

Anti-IL-6 Antibodies

Several malignancies are associated with IL-6 overexpression, and IL-6-mediated inflammatory pathways are correlated with cancer morbidity and mortality. For this reason, the blockade of IL-6 has been investigated as a possible anticancer treatment. Monoclonal antibodies against IL-6 or its receptor have been introduced for cancer therapy as single agents or in combination with chemotherapy. Data from preclinical studies and experimental trials, particularly in patients with advanced ovarian or lung cancer, revealed that, in addition to the anticancer effects, monoclonal anti-IL-6 antibodies can increase hemoglobin levels and improve anemia.[119,120]

Experimental Drugs Targeting Activin II Receptor Signals

Activin type II receptors, belonging to the family of serine/threonine kinase receptors, bind to a subgroup of transforming growth factor-β (TGF-β) and once activated, induce intracellular signals leading to the activation of SMAD2/3. The SMAD2/3 pathway is involved in proliferation and differentiation[121] and its activation in erythroid stem cells has an inhibitory effect on these processes.[122,123] Therefore, the TGF-β/activin II receptor pathway is a candidate therapeutic target to improve erythropoiesis. Among developed drugs targeting activin II receptor signaling, two fusion proteins obtained from the union of the activin II receptor extracellular domain and the Fc fragment of human IgG have been tested in clinical trials (luspatercept and sotatercept). These drugs act by binding to activin II receptor ligands, thereby limiting the negative effect of erythropoiesis of the SMAD pathway and increasing erythroid differentiation.[124,125] Luspatercept (ACE-536) has been approved by the FDA for the treatment of anemia in patients with β-thalassemia who require frequent red blood cell transfusions.[126] Phase-II and phase-III studies on the safety and efficacy of this compound for the treatment of anemia in myelofibrosis and myelodysplastic syndrome have been started.[127] Recently, the results from a Phase III study on patients affected by transfusion-dependent low risk myelodysplastic syndrome with ring sideroblasts, who were refractory to or unlikely to respond to ESAs or who had discontinued such agents owing to an adverse event, demonstrated that luspatercept reduced the severity of anemia and improved transfusion independence.[128] These results resulted in resulted in approval by both the US FDA and EMA.[129] Sotatercept (ACE-011) has been tested and is under investigation in pre-marketing clinical trials for various uses, including thalassemia and other congenital forms of anemia, myelodysplastic syndrome, multiple myeloma, end stage renal disease, and pulmonary arterial hypertension, with results indicating good tolerability and efficacy.[124,130] Interestingly, a Phase II placebo-controlled study evaluated sotatercept for the treatment of anemia associated with platinum-based chemotherapy in patients with advanced/metastatic solid tumors.[131] Various different doses were administered subcutaneously every 28 or 42 days for a maximum of four doses; 55 patients were enrolled, of which 50 received more than one dose of sotatercept and 5 received the placebo. Unfortunately, the

study was stopped early owing to a slow recruitment rate. The preliminary results indicated that mean hemoglobin levels increased 1 g/dL or more for the 66.7% of patients receiving 15 mg sotatercept and for the 38.9% of patients receiving 30 mg; the safety profile was comparable to that of placebo group.[131] These data, even if limited, highlight the potential clinical value of sotatercept for the treatment of anemia in patients with cancer.

Nutritional Support

As explained above, in cancer-related anemia, inflammation and metabolic changes seem to play crucial roles in the maintenance of low hemoglobin levels and weak erythropoietic responses. Several nutrients (such as amino acids and vitamins, mainly in group B) in addition to iron are essential for the synthesis of heme and hemoglobin and for erythropoiesis.[132] Furthermore, tumor-induced chronic inflammation is related to changes in energy metabolism towards an increase in calorie expenditure and is worsened by the decrease in nutrient intake under anorexia.[133,134] These observations emphasize the importance of careful evaluations of the nutritional status in patients with cancer and anemia and secondarily suggest that antioxidants, anti-inflammatory substances, and other specific nutrients may play key roles in the management of this condition. Notably, substances with anti-inflammatory /antioxidant activity are widely used in clinical practice. Rational supplementation should focus on nutraceuticals with efficacy supported by scientific evidence. Representative substances that have been studied in the context of chronic inflammatory or cancer anemia are described below.

Polyphenols

Polyphenols are plant-derived compounds with antioxidant, anti-inflammatory, and anti-infective properties. Clinical findings as well as in vitro and in vivo studies have shown that polyphenols can reduce pro-inflammatory cytokine production,[135,136] downregulate pro-oxidant enzymes, and upregulate antioxidant enzymes.[137] Curcumin is a well-known polyphenol extracted from turmeric. In addition to the cytokine-reducing effects common to other polyphenols, curcumin inhibits hepcidin transcription in -vitro.[138] In a randomized placebo-controlled trial, the administration of a single oral dose of 6 g curcuma induced a significant decrease in hepcidin levels.[139] Moreover, curcumin acts as an iron chelator in cell cultures and in mouse models.[140] Accordingly, curcumin may be useful in anemia characterized by iron overload or chronic inflammation, and a clinical trial evaluated the effect of curcumin on iron parameters in patients with thalassemia major, showing a decrease in serum iron, despite no changes in hepcidin levels.[141] In 2015, we published two case reports describing the successful management of two patients with anemia, one affected by advanced hormone-resistant prostate cancer and one with myelofibrosis and cachexia; using a multimodal approach consisting in rHuEPO, lactoferrin, curcumin, L-carnitine, and celecoxib, subjects showed improvements in hemoglobin levels, body weight, lean mass, fatigue, and QoL.[142,143]

Carnitine

L-Carnitine is an amino acid derivative synthesized by the body that acts as fatty acid transporter in the mitochondrion, allowing the production of energy by β-oxidation. Low carnitine levels are associated with fatigue in some cases, including in patients with cancer.[144,145] Thus, several trials have evaluated L-carnitine supplementation for the treatment of cancer-associated fatigue. We have previously conducted a randomized controlled clinical trial comparing megestrol acetate alone or with L-carnitine, celecoxib, and antioxidants for the management of cachexia induced by gynecological cancers. We found more pronounced improvements of lean body mass, fatigue, and QoL in the experimental arm, along with significative decreases in inflammatory and oxidative stress parameters.[34] Our results underline the usefulness of anti-inflammatory and antioxidant support for a more complete approach in cancer patients with advanced disease. In this regard, it must be remembered that fatigue is an extremely frequent symptom of advanced neoplasms and often accompanies cancer-related anemia. Another placebo-controlled study confirmed the positive role of carnitine supplementation in reducing fatigue, as evaluated by the Functional Assessment of Cancer Therapy-Anemia, in patients with advanced cancer with L-carnitine deficiencies.[146] Improvements in fatigue contribute to the general well-being of patients.

Vitamins

Some vitamins, such as folic acid (vitamin B9) or cyanocobalamin (vitamin B12), are indispensable for erythropoiesis and heme synthesis to the extent that deficiencies result in anemia. In view of the antioxidant effects and other

beneficial properties, several vitamins can be useful components of an integrated treatment strategy for anemia. Vitamin B9 and B12 are both enzymatic cofactors in nucleic acid synthesis; folic acid is also involved in amino acid metabolism and in oxidoreductive reactions.[147] Among other group B vitamins, thiamine (vitamin B1) is essential in energetic metabolism and glucose oxidation, as a cofactor for enzymes involved in the Krebs cycle.[148] Vitamin B6 is involved in basic cellular metabolism, amino acid and protein synthesis, and the neutralization of free oxygen radicals.[149] Interestingly, vitamin D has anti-inflammatory and immunomodulatory activities linked, for example, to its ability to

Table 1 Management of Chemotherapy- and Cancer- Related Anemia

	ESAs[a,b,c]	**Iron Supplementation**	**Other Supportive Agents**	**Novel Agents**	**References**
Absolute iron deficiency (ID): Ferritin < 30 ng/mL and TSAT < 20% CRP normal value	ESAs could be used after iron deficiency correction[26]	Oral iron supplementation or IV iron formulations (the choice depends on the severity of anemia and gastrointestinal absorption)[26,62,63,96]	Nutritional support (folate, vitamins B,C,D, polyphenols, L-carnitine, aminoacids)[156]	Oral iron liposomal formulation[161] Third generation IV iron formulations (ie, ferric carboxymaltose)[97,162,163]	[26,62,63,96,97,156,161–163]
Possible functional iron deficiency (FID): Ferritin 30–500 ng/mL and TSAT <50% High CRP	ESAs[26,62,63,96]	IV iron supplementation; oral iron is not indicated for gastrointestinal malasorbption[26,62,63,96]	Anti-inflammatory agents Nutritional support (folate, vitamins B,C,D, polyphenols, L-carnitine, aminoacids)[156]	Third generation IV iron formulations (ie, ferric carboxymaltose)[97,162,163]	[26,62,63,96,97,156,162,163]
Functional iron deficiency (FID): Ferritin >500–800 ng/mL and TSAT <50% High CRP	ESAs[26,62,63,96]	Supplementation with iron mobilizing agents such as lactoferrin should be preferred to IV iron[101,110]	Anti-inflammatory agents Nutritional support (folate, vitamins B,C,D, polyphenols, L-carnitine, aminoacids)[156]	Hepcidin antagonists[114]	[26,62,63,96,101,110,114,156]
Iron overload: Ferritin > 800 ng/mL and TSAT >50% High CRP	ESAs[26,62,63,96]	Supplementation with iron mobilizing agents[101,110] Oral or IV Iron supplementation is not indicated[26]	Anti-inflammatory agents Nutritional support (folate, vitamins B,C,D, polyphenols, L-carnitine, aminoacids)[156]	Hepcidin antagonist[114]	[26,62,63,96,101,110,114,156]

Notes: [a]ESAs are indicated only patients undergoing myelosuppressive treatment with palliative intent when Hb<10 g/dl.[26,62,63,96] [b]ESAs could be used in presence of chronic kidney disease (moderate to severe) independently from concomitant chemotherapy according to specific guidelines.[26] [c]In every category red blood cell transfusion may be indicated when Hb levels are <7–8 g/dl; it may be an option even at higher Hb levels (Hb <10 g/dl) depending on anemia-related symptoms and performance status, the severity of anemia and rate of Hb decline, and individual risk factors such as comorbidities (ie, bleeding, surgery, cardiovascular and ischemic disease).[26,62,63] References are indicated by superscript near to each statement and also in the last column.

Abbreviations: ESAs, erythropoiesis-stimulating agents; ID, iron deficiency; TSAT, transferrin saturation; CRP, C-reactive protein; IV, intravenous; FID, functional iron deficiency.

reduce cytokine and chemokine secretion.[150] Furthermore, it could have a role in the regulation of iron homeostasis. Notably, vitamin D-mediated reductions in IL-6 levels can affect hepcidin synthesis. In vitro studies have shown that vitamin D use is associated with a reduction in hepcidin and a rise in ferroportin expression in macrophages.[151] Clinical studies have revealed an association between chronic inflammatory diseases characterized by high hepcidin levels and a vitamin D deficiency.[152,153] Moreover, vitamin D administration decreases hepcidin concentrations in healthy adults[154] and hepcidin and inflammatory markers in patients with inflammatory bowel diseases.[155] These findings suggest that vitamin D could alleviate FID and related anemia in patients with cancer. A case–control study of patients with anemia due to congestive heart failure and catabolic disorder (attributed to a low albumin concentration), suggesting chronic inflammation, compared the use of IV standard iron therapy with iron plus supplementation with essential amino acids, group B vitamins (B1, B6, and B9), and vitamin D, for anemia treatment.[156] The increase in hemoglobin concentrations was significantly more rapid with supplementation than with iron alone, demonstrating the efficacy of integrated approaches to treat anemia in chronic inflammation. Finally, ascorbic acid (vitamin C) has relevant properties, including potent antioxidant activity and a role in iron metabolism, with the ability to enhance iron adsorption in the gut[157] and regulate cellular iron uptake.[158] In hepatocyte cultures, vitamin C induced a decrease in hepcidin production and upregulated EPO receptor expression.[159] In patients with advanced chronic kidney failure and EPO-resistant anemia, the addition of ascorbic acid to standard therapy with ESAs and IV iron leads to greater increases in hemoglobin levels and transferrin saturation compared to ESAs plus iron alone and a decrease in CRP concentrations, likely by improving ESA responsiveness.[160]

The same benefits achieved by supplementation could be obtained in patients with cancer and anemia. Combinations between these substances and standard therapies for anemia induced by cancer chemotherapies and cancer-associated chronic inflammation should be evaluated in detail.

Conclusion

Anemia in patients with cancer is a cause for concern owing to its prevalence and its effects on health status, QoL, and prognosis. In chemotherapy-induced anemia, anticancer treatments exert toxic effects on the bone marrow and, in some cases, the kidney. However, patients with cancer more frequently suffer from the more complex type of anemia due to chronic inflammation in response to the tumor, oxidative stress, malnutrition, and systemic metabolic changes. Thus, the treatment of cancer-related anemia should be individualized basing on the severity, iron homeostasis, nutritional status (including evaluation of folate, vitamin B12, albumin, and GPS) and, surely, associated inflammation. ESA and iron supplementation are the cornerstones of the treatment of anemia in cancer patients with specific indication based on the different treatment setting as reported in Table 1. Of relevance, we think that the best therapeutic approach is ultimately the correction of all pathogenetic mechanisms by a multitargeted strategy using in the most appropriate way the therapeutic devices indicated in this review.

Abbreviations

CI, confidence interval; CRP, C-reactive protein; CTCAE, Common Terminology Criteria for Adverse Events; EMA, European Medicines Agency; EPO, erythropoietin; ESAs, erythropoiesis-stimulating agents; FDA, Food and Drug Administration; FID, functional iron deficiency; GPS, Glasgow Prognostic Score; HIF, hypoxia-inducible factor; ID, iron deficiency; IL, interleukin; IFN-γ, interferon gamma; IV, intravenous; NCI, National Cancer Institute; QoL, quality of life; rHuEPO, recombinant human erythropoietin; ROS, reactive oxygen species; TNF-α, tumor necrosis factor alpha; VEGF, vascular endothelial-growth factor.

Acknowledgments

Work supported by Associazione Sarda per la Ricerca in Ginecologia Oncologica. The authors would thank Dr Paolo Cannas, General Manager of the "Azienda di Rilievo Nazionale ad Alta Specializzazione G. Brotzu", for the encouragement in the development of this research. The authors thank Dr Martina Mura for her technical assistance.

Author Contributions

All authors made a significant contribution to the work reported, in the conception, study design, execution, acquisition of data, analysis and interpretation; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare no conflicts of interest in this work.

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