

Management of Anemia in Cancer Patients

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ABSTRACT

Anemia is a frequent complication in cancer patients. Cancer-related anemia adversely affects quality of life and is associated with reduced overall survival. Reasons for anemia in cancer patients are decreased production of RBCs resulting from nutritional deficiencies; insufficient production of RBCs because of the presence of chronic disease; Cancer promotes inflammatory cytokine production, which suppresses erythropoiesis and erythropoietin (EPO) production; bone marrow infiltration by the tumor or bone marrow suppression resulting from anticancer treatment such as surgery, chemotherapy, or radiotherapy; and increased loss of RBCs caused by blood loss from the tumor, surgery, or hemolysis. Correction of anemia can be achieved by different methods. Treatment is aimed at increasing the oxygen-carrying capacity of the blood, reducing fatigue, and improving the patient's overall quality of life. Erythropoiesis-stimulating agents, iron supplementation, and red blood cell transfusions have all been recommended in different settings.

Key Words: Anaemia, Cancer, Erythropoiesis-Stimulating Agents.

Introduction

Introduction Anemia is common and can be profound in cancer patients. The prevalence of anemia in solid tumor patients is close to 40%.^{1,2} and the frequency of anemia increases with the duration of chemotherapy. In hematological malignancies, the prevalence of anemia is almost double that found in solid tumors.³ Chemotherapy is one of the most important causes of anemia in cancer patients and the association between dose and duration of chemotherapy with anemia is well known.⁴ However, the negative impact that anemia has on the cancer patient in terms of survival and quality of life (QoL) also deserves attention. According to the WHO⁵ and the National Cancer Institute, anemia is categorized into four categories according to the level of hemoglobin. Anemia results in a series of symptoms that can influence the physical and functional status of patients, negatively affecting their treatment and quality of

life (QOL). Symptoms of anemia include palpitations, fatigue, dyspnea, nausea, depression, heart failure, impairment of cognitive function and dizziness⁶ Anemia in Cancer Patients.

Anemia can compromise the delivery of sufficient amounts of oxygen to all cells, including tumor cells. This hypoxic condition can worsen the results of radiotherapy and chemotherapy, because low tissue oxygenation is associated with a reduced sensitivity of tumors to radiation and some forms of chemotherapy, contributing to the progression of cancer and reduction in survival.^{7,8} Furthermore, there is abundant evidence suggesting that hemoglobin levels of less than 12 g/dl result in worse QOL and functional status for cancer patients when compared with higher levels. Present treatment options for anemia include blood transfusions, iron supplementation when there is iron deficiency or erythropoiesis-stimulating agents

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(ESAs), such as recombinant human erythropoietin (EPO) and darbepoetin- α .⁹ Given the impact of anemia on the survival of cancer patients, the management of anemia has been explored in several clinical trials to date.¹⁰ Blood Transfusions.

The use of blood transfusions to correct anemia is a therapeutic modality for which there is less literature available for patients with cancer. Consequently, few studies are able to provide high-level evidence on the efficacy and safety of this modality. The chief aim of transfusion is to immediately correct the signs or symptoms resulting from anemia.¹¹ Typically, there is a growing need for blood transfusions in individual cancer patients as the number of chemotherapy cycles administered increases. However, there is wide variation in the level of hemoglobin that triggers blood transfusions among the various studies and among different types of cancers.¹²

There is general medical consensus that blood transfusion should be used in patients with terminal illness when there is acute blood loss or chronic deterioration of the patient, when hemoglobin levels are below 7 g/dl, in anemic patients with respiratory or heart symptoms or in patients with anemia due to chemotherapy.¹³ However, the trigger level of hemoglobin and its target values have not been determined. On the other hand, the EORTC guidelines mention that patients with hemoglobin levels of less than 9 g/dl should primarily be evaluated for the need of transfusions.¹⁴ The ASH/ASCO guidelines suggest that blood transfusions may be an option for the correction of anemia associated with chemotherapy when hemoglobin levels are less than 10 g/dl or for elderly patients with limited cardiopulmonary reserve, patients with coronary disease or symptomatic angina, those with substantial reduction in exercise capacity or those with difficulty in performing daily activities.¹⁵

The results of a number of studies evaluating the impact of transfusion on mortality in critically ill patients are conflicting. One study of 56 esophageal cancer patients receiving chemoradiation therapy demonstrated that blood transfusions increased overall survival.¹⁶ However, there is evidence in the literature that blood transfusion may have a negative impact on the progression of disease.¹⁷ Fyles and colleagues

analyzed the published data from a randomized trial and found that transfusion in anemic patients with cervical cancer did not result in benefit.¹⁸ In a retrospective study of 70,542 patients hospitalized with cancer, the use of blood transfusion was associated with higher rates of venous and arterial TEEs, in addition to an increased risk of hospital mortality.¹⁹ However, the causal relationship could not be established owing to the retrospective nature of the study. There are other potential hazards related to blood transfusion. Some of the currently known blood contaminants include hepatitis A virus, cytomegalovirus, Epstein-Barr virus, human herpesvirus 8, *Toxoplasma gondii*, parvovirus B-19, West Nile virus, spongiform encephalopathy prions, *Trypanosomacruzi*, *Babesia* species and *Plasmodium* species, although the introduction of numerous safety interventions for infectious organisms has dramatically decreased the incidence of transfusion-related infections.^{20,21} Other transfusion reactions include febrile nonhemolytic transfusion reaction, bacterial infection, acute hemolytic reaction, anaphylactic reaction, transfusion-associated acute lung injury, volume overload, iron overload, delayed hemolytic reaction, transfusion-associated graft-versus-host disease and post-transfusion purpura.²² At present, blood transfusion is not a proven safe alternative to ESAs, as comparative studies have not been performed and, in contrast to ESAs, little is known about the

Epidemiology

Anemia is one of the most frequent manifestations in patients with cancer. In fact, it has been shown that 30% to 90% of all cancer patients are anemic, a figure that is dependent upon the type of cancer and the definition of anemia used.²³ The incidence and severity of the anemia depend upon a number of factors, which are listed in TABLE 1.^{24,25}

Table 1: Factors Contributing to the Incidence and Severity of Anemia

Type of malignancy
Extent of malignancy
Type, schedule, and intensity of therapy used to treat the cancer
Patient age
Patient gender
Presence of comorbid conditions
Any other medications the patient is taking

Pathophysiology

Anemia is the result of a combination of decreased circulating erythrocytes, reduced packed cell volume, and reduced Hb levels.²⁶ This can occur through various pathophysiologic mechanisms including excess loss of blood, increased destruction of RBCs, and decreased erythropoiesis.

Erythropoietin (EPO), vitamin B₁₂, folic acid, and iron are essential for erythropoiesis. Erythropoietin controls the maturation, differentiation, and survival of erythroid cells during this process.²⁷ EPO is primarily produced by the kidneys and transported to the bone marrow.²⁸

Abnormal iron metabolism or retention of iron in the macrophages reduces the amount of iron that is available for erythropoiesis. The altered metabolism of iron is primarily caused by hepcidin, a protein that decreases the absorption of iron in the intestines as well as the release of iron by the macrophages. The production of hepcidin is increased by cytokines released from tumors, thereby decreasing the amount of circulating iron. It has also been shown that the production of cytokines such as interleukin (IL)-6 is increased by certain chemotherapeutic regimens.²⁵ Repeated cycles of chemotherapy may worsen the reduction in erythropoiesis cumulatively.²⁸

As oxygen delivery is diminished, the body's tissue cells become hypoxic, resulting in a series of physiological responses as the body attempts to gain or maintain tissue oxygenation. It is thought that the normal utilization of iron in cancer patients may be interrupted by an interaction between the tumor cells and the host's own immune system. This interaction leads to the up-regulation of specific inflammatory cytokines such as IL-1, gamma interferon, and tumor necrosis factor alpha (TNF- β), which decrease differentiation of erythroid precursors in the bone marrow, interfere with normal iron utilization, and inhibit normal hypoxia-driven erythropoietin production. Nephrotoxic chemotherapeutic agents may worsen the problem by causing renal impairment.

In chronic anemia, tumors have been shown to release an anemia-inducing factor, a molecule that

reduces the life span of erythrocytes. This exacerbates anemia to the point where erythropoiesis cannot compensate for the inferior survival of the RBCs.²⁹

Risk Factors for Anemia in Cancer

The following risk factors have been identified for anemia in cancer³⁰:

- Myelosuppressive chemotherapy or radiation therapy
- Low Hb levels (10-12 g/dL) at the initiation of cytotoxic chemotherapy
- Administration of platinum-containing regimens, which also increases the need for transfusion support.

Treatment

Apart from an overall improvement in the patient's quality of life, treatment of anemia is essential for a number of reasons. Anemia compromises the delivery of sufficient amounts of oxygen to all cells, including tumor cells.²⁸ Since low tissue oxygenation is associated with a reduced sensitivity of tumors to radiation and other forms of chemotherapy, the efficacy of these treatments is reduced in anemia.^{31,32}

The goal of therapy should be to increase the oxygen-carrying capacity of the blood and treat the underlying cause. Underlying conditions such as nutritional deficiencies are easier to treat than others, such as occult blood loss. Various options are available for the management of cancer patients with anemia. These include³³

- Appropriate supplemental therapy with folic acid and/or vitamin B₁₂ to correct nutritional deficiencies
- Erythropoiesis-stimulating agents (ESAs)
- Iron supplementation
- Blood transfusions, which are indicated for patients with acute severe blood loss. For patients whose anemia is chronic, erythropoietic agents are preferred.

Erythropoiesis-Stimulating Agents: ESAs, including recombinant human erythropoietin alfa (rHuEPO; Procrit, Epreon) and darbepoetin alfa

(Aranesp), were traditionally developed for the management of anemia in patients with chronic renal failure. They have demonstrated similar efficacy and limitations when used in comparable doses in cancer patients with anemia.²⁵ ESAs are indicated for the management of patients whose endogenous EPO levels are abnormally low, as the ESA mode of action and immunologic and hematologic effects are similar to those of endogenous EPO.³⁰ Studies conducted on rHuEPO have shown that it improves patients' Hb levels and quality of life and decreases transfusion requirements.^{33,34} It has been proposed that ESAs also improve the cognitive function of patients receiving chemotherapy.³⁵

A systemic review conducted by the American Cancer Society showed that optimal clinical benefit from erythropoietic treatment of chemotherapy-induced anemia may be achieved through early intervention.³⁶ There is clearly a benefit of using ESAs; however, all other causes of anemia should be investigated and corrected prior to the use of ESA therapy.

Darbepoetin and rHuEPO are both indicated for the treatment of anemia in patients with nonmyeloid malignancies in whom anemia is related to chemotherapy.²⁵ The American Society of Hematology (ASH) and the American Society of Clinical Oncology (ASCO) recommend that treatment be initiated when Hb levels drop below 10 g/dL and the dosage be reduced if there is a minimum increase of 1 g/dL in Hb levels by 2 weeks.³⁷

The aim of the therapy should be to raise the Hb to the lowest concentration to avoid transfusion. If the minimal increase of 1 to 2 g/dL of Hb is not achieved after 6 to 8 weeks of treatment, the ESA therapy should be stopped.³⁶ While it is difficult to predict patient response to these therapies with the current data, it has been shown that approximately 50% to 60% of patients demonstrate a 2 g/dL increase in Hb when treated with rHuEPO.³⁰ ESA therapy should be discontinued upon completion of the chemotherapy course.^{38,39}

The recommended dosage for darbepoetin alfa is 2.25 mcg/kg as a weekly subcutaneous (SC)

injection. If the Hb levels do not rise by at least 1 g/dL after 6 weeks, the dosage should be increased to 4.5 mcg/kg. If the Hb levels increase more than 1 g/dL in a 2-week period or if Hb exceeds 12 g/dL, the dosage of darbepoetin should be reduced by 40%.³⁸ Darbepoetin should be stopped if Hb levels rise above 13 g/dL.³⁰

The recommended dosage of rHuEPO is 40,000 U administered SC once weekly or 150 U/kg administered SC three times a week in patients whose Hb levels are below 10 g/dL. The dosage of rHuEPO should be reduced by 25% if the Hb level increases >1 g/dL in any 2-week period or reaches a level needed to avoid RBC transfusion.³⁹

ESAs are packaged in a vial that should not be shaken, as they will denature.^{38,39} The contents of the vial should not be diluted or pooled. The risks of ESA therapy should also be taken into consideration. ESAs are thought to increase adverse cardiovascular events, enhance the risk of venous thromboembolism, shorten the time to tumor progression, and reduce survival in anemic cancer patients through different mechanisms.^{40,41} For this reason, the use of ESAs is discouraged in cancer patients who are not undergoing treatment with chemotherapy or radiotherapy.⁴² All ESAs come with a black box warning about increasing the risk of death, myocardial infarction, stroke, venous thromboembolism, thrombosis of vascular access, and tumor progression and recurrence.^{20,21/37,38} The ESA APPRISE Oncology Program has been set up by the FDA to advise patients, caregivers, and healthcare professionals on the safe use of ESAs.⁴³

Iron Supplementation: Iron supplementation, preferably parenterally, is indicated in patients with low levels of ferritin (<30 ng/mL), transferrin saturation (TSAT <15%), and low (<26 pg/cell) reticulocyte Hb content (CHr). Two types of iron deficiency have been recognized in anemic cancer patients:

- Absolute iron deficiency (AID) that occurs with chronic bleeding due to, for example, GI or gynecologic lesions, blood loss from surgery, nutritional deficiencies, and anemia of chronic disease (ACD). It is defined as a serum ferritin level of <30 mcg/L and decreased TSAT of <15%.^{1/43}
- Functional iron deficiency (FID) that arises after

continued erythropoietin use. It is the most common cause of an inadequate response to ESA therapy, particularly in patients with renal failure. Therefore, most patients on ESA therapy will eventually require iron supplementation.^{6/26}

Iron supplementation was introduced when ESA therapy alone demonstrated poor response rates in chemotherapy-treated patients.¹ The efficacy of a combination of IV iron and ESA therapy was tested and the role of iron in functional iron deficiency was established.¹ While current evidence supports the use of IV iron supplementation to improve hemoglobin responses in anemic patients with cancer, prospective studies on the long-term efficacy and safety of IV iron are needed. Furthermore, optimal dosing regimens need to be established.²⁵

Iron can be administered orally or as parenteral formulations of low-molecular-weight (LMW) iron dextran, ferric gluconate, and iron sucrose. Parenterally administered iron has a superior response when compared to oral iron.²⁶ The latter is therefore rarely used in cancer patients with anemia and is not discussed in this article. Test doses are recommended for iron dextran. Patients who have exhibited previous sensitivities to iron dextran or other IV iron preparations or those who have multiple drug allergies should also be administered a test dose.

Table-2: Shows the dosing regimen for IV iron supplementation.²⁶

Table 2. Recommended for IV Iron Supplementation

Iron Preparation	Test Dosage	Treatment Dosage
Iron dextran	2.5 mg given via a slow IV push; wait 1 h before given full dose	100mg IV given over 5 min; repeated weekly for 10 dose or total dosage (1g) given over several hours as an infusion
Ferric gluconate	2.5 mg given via a slow IV push or infusion	125 mg given via IV over 60 min; repeated once a week for a total of 8 doses
Iron sucrose	2.5 mg given via a slow IV push	200 mg IV given over 60 min, repeated doses given every 2-3 wk or 200 mg IV given over 2-5 min; repeated dosing given every 1-4 wk

min: minute. Source: Reference 6.

Parenteral iron is associated with hypotension, nausea, vomiting and/or diarrhea, pain, hypertension, dyspnea, pruritus, headache, and dizziness. Furthermore, it can be inconvenient to administer and costly³⁰ Since high-molecular-weight (HMW) iron dextran is associated with a

higher incidence of adverse events than LMW iron dextran, the latter is preferred overall.^{6/26}

Red Blood Cell Transfusion: RBCs are the preferred blood product for transfusions to correct anemia in cases of acute anemia after hemorrhage. Certain patients may require an infusion that is cytomegalovirus negative. The aim of using an RBC transfusion is to treat or prevent a deficiency in the oxygen-carrying capacity of the blood, and transfusion is not usually indicated if the patient's Hb level is ≥ 10 g/dL.²⁶

RBC transfusions offer the advantage of a rapid increase in Hb and hematocrit levels immediately upon infusion. It is estimated that a transfusion of 300 mL (1 unit) of pure RBCs will result in an average increase of 1 g/dL of Hb or 3% of hematocrit in an otherwise normal adult who does not experience simultaneous blood loss. This leads to an overall rapid improvement in fatigue.²⁶

The patient's blood must be cross-matched for ABO compatibility before the RBCs can be transfused. If the patient requires repeated infusions, the risk of adverse reactions can be minimized by the use of leukocyte-reducing blood and premedication with an antihistamine or acetaminophen.²⁶

RBC transfusion is not without risks, including the potential for transfusion-transmitted infectious agents, transfusion reactions, alloimmunization, and immunosuppression.³⁰ Other risks of transfusion include congestive heart failure, increased thrombotic events, and iron overload.²⁶ It is useful to note, however, that patients requiring RBC infusions during the period corresponding to chemotherapy treatment only are highly unlikely to experience iron overload.²⁶

Conclusion

Anaemia is a major cause of morbidity in patients with cancer. The severity and prevalence of the condition varies based on a number of factors. The aim of treatment is to increasing the oxygen-carrying capacity of the blood and also reducing fatigue, and improving the patient's overall quality of life. The impact of early intervention is to improved on quality of life and on the ability to maintain chemotherapy and radiotherapy schedules.

Conflict of interest: none.

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