

Epoetin 2000 I.U. SEDICO & 4000 I.U. SEDICO  
&  
Anemia of Chronic Renal Failure & In Cancer Patients

ANEMIA...



AN EASY APPROACH  
TO A TOUGH PROBLEM

**Anemia of Chronic Renal Failure**

*The association of chronic renal failure and anemia has been recognized since the early 19th century; nowadays such a manifestation is regarded as one of the many components of the vast array of signs and symptoms present in patients with chronic renal failure. The introduction of dialysis brought new insights to this complex subject, but also added new mechanisms for the development or aggravation of such clinical picture.*

*The anemia of renal failure is usually characterized by normochromic and normocytic blood cells. There is usually hypoplasia of the erythroid precursors in the bone marrow with little or no interference with normal leucopoiesis and megakaryocytopoiesis. On blood smears one may find typical, although not exclusive, spiculed and deformed red cells (burr cells or echinocytes). The anemia aggravates as the renal function further declines, and the hematocrit may reach levels as low as 20% or 15%. As with any chronic anemia, compensatory mechanisms come into play in order to maintain acceptable levels of tissue oxygenation, and they consist mainly of increased levels of 2,3 DPG, lowered peripheral vascular resistance and an elevated cardiac output (in the absence of previous cardiac disease).*

## **Pathophysiology :**

*If the blood volume is constant, and blood loss is absent any case of anemia can only be explained by decreased production of erythroid precursors or increased destruction. Both processes seem to be operating in renal failure.*

### **► Increased destruction:**

*Many studies have shown an inverse correlation between the red cell survival and serum blood urea nitrogen concentration. This could be demonstrated by the classical study where red blood cells from uremic individuals showed a normal life span when injected in normal individuals, the inverse (shortened red cell life span) could be demonstrated when erythrocytes from normal individuals were injected in uremic patients. The most convincing demonstration that specific toxins (not necessarily urea) were the responsible for the shortened red cell survival was obtained with the introduction of dialysis.*

*Dialysis improved, to a limited extent, the anemia in chronic renal failure patients, although this finding could not be ascribed to prolonged red cell survival; rather, a better utilization of iron (not increased serum levels) and red cell production seemed to be determinant. The patients showed diminished transfusion requirements after initiation of a dialysis program.*

*Besides the mechanisms described above, the therapy itself (dialysis) can be responsible for increased destruction of red blood cells, further aggravating the anemia. Haemodialysis can worsen the anemia due to the procedure associated blood losses and mild effect on oxygen transporting function. Hypersplenism may, rarely, be associated with chronic dialysis leading to a sequestration of erythrocytes and further destruction of circulating red cells. If hypersplenism proves to be an important problem splenectomy may be considered, since it has been shown to cause a decrease in transfusion requirements.*

### **► Decreased Red Blood Cell Production:**

*Decreased red blood cell production in the critically ill patient is attributed to low concentrations of erythropoietin, blunted response to erythropoietin, inflammatory cytokines, immune-mediated functional iron deficiency, and other nutritional deficiencies.*

**Erythropoiesis:** *is the development of mature erythrocytes (red blood cells). A decrease in oxygenation to the tissues signals the kidneys to increase production and release of erythropoietin, stimulating stem cells to differentiate into preerythroblasts and erythroblasts, increasing the release of reticulocytes and their subsequent maturation into erythrocytes.*

*Under normal conditions serum erythropoietin concentrations are increased by bleeding and decreased after transfusion; actually in nonuremic patients it may increase up to 100 times its normal value. In uremic patients the normal response to hypoxemia (increased secretion of erythropoietin) is partially, but not completely, blunted. These individuals show increased levels of the glycoprotein after hemorrhage or hypoxic crisis, although the levels are not even close to those of a normal individual. Therefore, the stimulus to erythropoiesis is not sufficient in uremic patients.*

## **Management of anemia:**

*The mainstay of the treatment of anemic patients is the use of "Recombinant human erythropoietin (rHuEPO)". The response to treatment is impressive and the need for transfusion is importantly decreased.*

*Upon initiation of therapy a target hematocrit should be set as well as the iron stores should be completely evaluated (since low stores may blunt the proliferative response to erythropoietin).*

The beginning of therapy should be gradual to avoid excessively rapid increases in the red cell mass with its hyperviscosity consequences. A total weekly dose of 110 to 120 U/kg divided into two or three subcutaneous injections is an adequate therapeutic regimen.

Transfusions should be avoided as much as possible, not only because of the well known infectious risks and the fluid overload in cardiac patients but also to avoid inhibition of the low, although present, positive feedback on erythropoietin secretion exerted by chronic hypoxemia.

Other possible deficiencies should be assessed before therapy is started such as, **vitamin B12 deficiency, Folate deficiency or Aluminum intoxication** (this latter leading to microcytic anemia). Throughout the course of therapy, iron stores (serum iron, ferritin and TIBC) should be determined frequently, since the rapid proliferative response may not be accompanied by an adequate availability of iron. If the iron stores are proved insufficient during the course of therapy, replacement should be started without delay.

### **Adverse effects:**

#### **Some adverse effects have been documented in patients receiving rHuEPO:**

- ▶ Myalgia and influenza-like symptoms may occur.
- ▶ The occurrence of seizures remains an unsettled issue, with some defending a causal relationship, while others argue against this hypothesis suggesting that these neurological phenomena are due to imbalances in dialysis therapy.
- ▶ Thrombotic events **are not** increased with the use of rHuEPO, although clotting within the dialyser may occur.
- ▶ Hypertension is without any doubt the most important not only in terms of frequency but also morbidity. Occurring in approximately 30% to 35%, hypertension usually occurs in the first 4 months of treatment while the hematocrit is increasing. The exact mechanism of hypertension is not defined yet but it may be so severe as to cause hypertensive encephalopathy with headache, visual disturbances and seizures. Uncontrolled hypertension is a contraindication to the initiation of therapy with rHuEPO. Hypertension is not dependent on the dose of rHuEPO or the rate of hematocrit increase.

**Bernardo Boaventura Liberato**

#### **References**

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- 3) Naets JP - *Hematologic disorders in renal failure- Nephron, 14:2,181-94:1975*
- 4) Paganini EP - *Overview of anemia associated with chronic renal disease- Semin Nephrol,9:1Suppl 1, Mar3-8:1989*

# **Anemia in Cancer Patients**

## **Introduction and Overview**

**Hussain I. Saba, MD, PhD**

### **Introduction**

Anemia is a common complication of malignancies. Because its causes and mechanisms are complex, the term “multifactorial” has been applied. Cancer-related anemia may occur as a direct effect of the neoplasm, it may be due to products of the cancer, or it may develop as a result of the cancer treatment itself. In the past, anemia occurring in cancer patients was often referred to as “chronic anemia” or “anemia of chronic disease.” These effects may be reflective of a paraneoplastic syndrome.

#### **Anemia Occurring as a Direct Effect of the Neoplasm**

Direct-acting factors due to the effects of the cancer are summarized in Table 1. Notable among these are solid tumor malignancies, such as breast and prostate cancer, that invade the marrow. Often overlooked as factors in inducing anemia, these malignancies produce a desmoid or fibrotic reaction, with increased marrow fibrosis that results in alteration of marrow space and sinusoidal matrix. This can affect the orderly release of mature blood cells from bone marrow and can produce a leukoerythroblastic picture with immature red cells and early myeloid white cells seen in peripheral blood.

**Table 1. -- Anemia of Cancer: Direct Effects of the Neoplasm**

<b>Exogenous Blood Loss (Acute Or Chronic):</b>	Gastrointestinal malignancies Head and neck cancer Genitourinary cancers Cervical and vaginal cancers
<b>Intratumor Bleeding:</b>	Sarcomas Bulky melanomas Hepatoma Ovarian cancer Adrenocortical tumors
<b>Anemia Due To Erythrophagocytosis:</b>	Histiocytic medullary reticulosis Histiocytic lymphomas Other histiocytic neoplasms
<b>Bone Marrow Replacement:</b>	Leukemias Lymphomas Myelomas Carcinomas (breast, prostate)

Direct causes of anemia in malignancy include known substances or proteins produced by the cancer (Table 2). The deposits of amyloid in myelomas and amyloidosis can be extensive enough to replace the bone marrow. The development of antibodies in chronic lymphocytic leukemia, lymphoma, and sometimes solid tumor malignancies can lead to immune hemolytic anemias. Furthermore, development of microangiopathic hemolytic anemia, which is seen in some solid tumor malignancies, may result from procoagulants released from cancers.



## **Impaired Iron Utilization in the Anemia of Cancer:**

Impairment of iron metabolism and depressed erythropoiesis constitute primary hallmarks as well as the basis for anemia in cancer patients. Although most studies were conducted in chronic inflammatory states such as rheumatoid arthritis rather than the anemia of cancer, it is now clear that several cytokines produced in cancer patients (eg, TNF, IL-1, IL-6, transforming growth factor-beta, interferon-gamma, and EPO) are responsible for suppressed erythropoiesis and impaired iron metabolism.

It is not yet known whether different cytokines or different sequences of cytokine release are critical to specific lesions. TNF increases in patients with cancer. In the animal model, TNF administration has resulted in changes of iron metabolism characteristic of the anemia of malignancy. Furthermore, injection of TNF in human patients with metastatic cancer has resulted in the expression of all of the features of impaired iron utilization. IL-1 has been implicated in suppression of erythropoiesis in inflammatory lesions, like rheumatoid arthritis, but its role in anemia of malignancy in humans has not yet been delineated. Other cytokines such as IL-6 and transforming growth factor-beta also suppress erythropoiesis and iron metabolism, but their exact roles have not yet been determined.

Thus, it appears that anemia in cancer patients can be defined as a "cytokine-associated syndrome" in which multiple cytokines interact to produce suppression of erythropoiesis and derangement of iron metabolism. Some scientists have suggested that the term "anemia of malignancy" should be replaced with the term "cytokine associated anemia" and the primary involved cytokine should be delineated by an appropriate subscript. More studies are underway to understand the critical interaction of these cytokines, their production, their release, and their temporal relationship with each other in cancer patients. It is not known whether specific cytokines are related to specific neoplasms. With this information, the true mechanism of anemia in cancer patients will be clearly understood and appropriate management strategies can be developed.

## **Therapy of Anemia of Malignancy**

Although therapy for the anemia of malignancy has been focused on treating the underlying malignancy, there have been reports of improved red cell mass with EPO administration in cancer patients undergoing radiation therapy and chemotherapy, such as cisplatin and carboplatin. Investigators have also reported improvements in the quality of life associated **with EPO administration**. The Ludwig group reported experience with EPO in 63 patients with myelodysplastic syndrome and multiple myeloma. Response, as measured by raising hemoglobin to 2 g/dL above the baseline, was seen in 43% of patients. Experience with patients with nonmyeloid malignancies receiving cancer chemotherapy in community oncology practice in the United States demonstrates that responses occur in 50% to 60% of EPO-treated patients, and the response rate is over 75% in patients with  $\geq 1$  g/dL decrease in hemoglobin.

→ In a Japanese study, head and neck cancer patients undergoing radiation therapy exhibited increased hemoglobin levels with successive EPO injections.

→ Two sequential trials in ovarian cancer patients treated with carboplatin and etoposide, with and without EPO, showed improvement in hemoglobin levels in the EPO-treated group.

→ Preliminary analyses of randomized open-label trials of EPO with radiation therapy in patients with lung, breast, and prostate cancer also have shown increases in mean hemoglobin levels during treatment. Additional randomized, controlled studies are needed to clearly define the efficacy of EPO in the management of anemia in cancer patients.

## **Conclusions**

Anemia, a common occurrence in malignant disease, can be the first diagnostic clue to suggest a malignant disease. It also can create a disabling burden for patients already coping with cancer. Because a number of underlying mechanisms may contribute to the anemia of cancer, it is important to define causes that are treatable. As our understanding of this phenomenon increases, researchers are beginning to appreciate the role played by tumor-associated cytokine production in the development of anemia of malignancy.

The availability of recombinant EPO is a significant addition to the therapeutic armamentarium. Many of these

issues are further described in this supplement, which distills the proceedings of a roundtable discussion of experts held in Key West, Florida, in October 1997.

#### **Suggested Readings**

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## **Epoetin 2000 & 4000 I.U.SEDICO**

#### **Composition:**

Each 1 ml of the solution contains:

Recombinant erythropoietin..... 2000 or 4000 units.

#### **Indications:**

- ▶ Treatment of anemia of chronic renal failure patients, including those on dialysis and those who are not.
- ▶ Treatment of anemia in HIV patients treated on Zidovudine.
- Treatment of anemia in Cancer patients on chemotherapy
- Reduction of allergenic blood transfusion in surgery patients



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#### **Dosage and administration:**

##### **▶ Chronic renal failure patients:**

Doses over the range of 50-100 units / Kg three times weekly have been shown to be safe and effective. The dose should be reduced as the hematocrit approaches 36% or increased by more than 4 points in any two week period. The dose must be individualized to maintain the hematocrit within the suggested target range.

##### **▶ Zidovudine-treated HIV infected Patients:**

The recommended starting dose is 100 units / Kg as an IV OR S.C injection three times weekly. If the hematocrit exceeds 40% the dose should be discontinued until the hematocrit drops to 36%.

##### **▶ Cancer patients on chemotherapy:**

The recommended starting dose is 150 units / Kg S.C Three times weekly. Dose adjustments may be required if the response is not satisfactory, the dose can be increased up to 300 units / Kg three times weekly. If the hematocrit exceeds 40% the dose should be discontinued until the hematocrit drops to 36%

##### **▶ Surgery patients:**

The recommended dose is 300 units / Kg / day S.S for 10 days before surgery, on the day of surgery, and for four days after surgery.