Clinics of Oncology

Research Article ISSN: 2640-1037 | Volume 6

Anemia in The Patient with Cancer

Hunis A[*1] and Hunis M[2]

[1]School of Medicine, Buenos Aires University, Argentina

[2]School of Medicine, Maimonides University, Argentina

[*]**Corresponding author:**

Adrian Hunis,
School of Medicine, Buenos Aires University, Argentina, E-mail: ahunis@fmed.uba.ar

Received: 05 Jun 2022
Accepted: 18 Jul 2022
Published: 22 Jul 2022
J Short Name: COO

Citation:

Hunis A. Anemia in The Patient with Cancer. Clin Onco. 2022; 6(9): 1-11

Keywords:

Cancer; Kidney disease; Normochromic

1. Abstract

Anemia is a common condition of cancer patients. This is because cancers cause inflammation that decrease red blood cell production. In addition, many chemotherapies are myelosuppressive, meaning they slow down the production of new blood cells by the bone marrow.

In other cases, anemia is caused by kidney disease. The kidneys produce a hormone that spurs the bone marrow to make red blood cells. If a patient has kidney cancer or if the kidney is impacted by cancer treatment, he or she could develop anemia.

Anemia can also be caused by the loss of blood cells due to bleeding.

2. Introduction

2.1. Anemia of chronic disorders

Anemia of chronic disorders or simple chronic anemia (ACS) represents one of the most frequent causes of anemia in clinical practice.

It accompanies a variety of inflammatory conditions such as infections, rheumatic diseases, and neoplasms, and responds to a multifactorial etiopathogenesis that includes four fundamental mechanisms.

− abnormalities in iron utilization

− decrease in the half-life of RBCs

− direct inhibition of hematopoiesis

− relative deficiency of erythropoietin (EPO)

It is from the end of the 1980s when the role of various cytokines in the pathogenesis of the entity is recognized, and it is currently considered a true “cytokine-associated syndrome”.

3. Clinical and Cytomorphological Aspects

Anemia is hypo regenerative with the following characteristics:

− Of moderate intensity and oligosymptomatic. The hematocrit is higher than 30% in most patients1, although approximately a quarter of them may present more severe forms of anemia,

− Normocytic and normochromic, approximately one third of cases may show MCV less than normal.

− Low serum iron contrasting with normal or high deposits,

− Underlying diseases include:

− Active infections

− Chronic inflammations (example: collagen diseases)

− Neoplasms

− Other conditions: alcoholic liver disease, congestive heart failure, thrombosis, chronic lung disease, diabetes, etc.

4. Etiopathogenesis

As previously mentioned, ACS responds to four fundamental physio pathogenic mechanisms: (Table 1).

Table 1: Anemia of chronic disorders. Physio pathogenic mechanisms

1	Iron utilization abnormalities
2	Decrease in the half-life of RBCs
3	Direct inhibition of hematopoiesis
4	Relative deficiency of erythropoietin (EPO)

4.1. Alterations in Iron Metabolism

a. Low serum iron with increased iron stores,

b. Less iron absorption.

c. Shortening of the serum half-life of iron.

d. Decrease in the release of iron from its deposits, which would decrease both plasma levels and the iron available to be incorporated into erythropoiesis.

We will stop to analyze iron metabolism alterations in more depth, since the ACS highlights the relationship between iron metabolism and immunity.

Iron is a fundamental component for all living cells, since it is a cofactor for the enzymes of the mitochondrial respiratory chain, the citric acid cycle, DNA synthesis, as well as a fundamental component for the transport of O2 through hemoglobin and myoglobin. On the other hand, the intracellular accumulation of metabolically active iron can be deleterious for the surrounding cells and tissues, since it is capable of catalyzing the formation of highly toxic hydroxyl radicals. That is why a delicate regulation of iron homeostasis is essential for the maintenance of cellular functions as well as to avoid cell damage.

4.1.1. Iron Homeostasis

The maintenance of iron homeostasis is regulated at the post-transcriptional level through the interaction of cytoplasmic proteins called IRON REGULATORY PROTEINS (IRP) 1 AND 2, which interact with ring structures of messenger RNA (mRNA) called RESPONDING ELEMENTS. TO THE IRON (IRE).

4.1.2. IREs Are Located

− at the 5’ end of the heavy and light chain mRNA of ferritin (core iron storage protein)

− at the 5’ end of the mRNA of erythroid amino levulinic acid synthetase or e-ALA (central protein of iron consumption since it is the key enzyme in heme synthesis)

− at the 3’ end of the transferrin receptor mRNA (the most important protein for iron entry into the cell)

Cellular iron deficiency stimulates the binding of IRPs to IREs, which determines the blockage of ferritin and e-ALA expression, and an increase in the expression of the transferrin receptor. In contrast, the increase in metabolically active intracellular iron reduces the affinity for the IRP-IRE binding, which determines a stimulus for the synthesis of ferritin and e-ALA, while the transferrin receptor mRNA is degraded by RNAses by losing the protection conferred by its union with IRP. The affinity of the IRP-IRE bond is not only regulated by iron needs, but also depends on the production of free radicals by activated immune cells (nitric oxide and hydrogen peroxide).

Likewise, a set of cytokines can affect iron homeostasis, either by altering the production of these radicals that they modify IRP affinity, or by inducing independent IRP/IRE regulations that affect the transcription and translation of critical proteins such as ferritin or the transferrin receptor. Numerous recent publications have highlighted the role of hepcidin in the regulation of iron homeostasis. Hepcidin, a 25 amino acid peptide produced in the liver, which was described by Tomas Ganz, is currently considered a mediator of natural immunity and a regulator of iron 7 homeostasis. Its synthesis is stimulated by inflammation and by the amount of deposit iron. In transgenic murine models, it has been shown that hepcidin plays an important role in the regulation of iron metabolism, since it inhibits its absorption in the small intestined08, its transport through the placenta, and its release from macrophages. Supporting these findings, hepcidin gene mutations have been found in members of two families with severe juvenile hemochromatosis, with affected patients being homozygous for the mutation. Also, it has been shown that a poor hepcidin response to iron deposition could contribute to iron overload in the more common moderate forms of hemochromatosis.

Although it is accepted that hypoferremia is a common response to infection and/or generalized inflammatory processes, and that its development in these circumstances requires the synthesis of hepcidin, it is not clear which of the inflammatory mediators that regulate this synthesis. In this sense, the studies carried out by Nemeth et al., both in human hepatic cell lines, as well as in murine models and in volunteers, seem to indicate that 1L-6 would be necessary and sufficient by itself to induce hepcidin synthesis, which would increase more than 100 times in anemia of inflammation. This would explain the sequestration of iron in the system.

Soon, the discovery of hepcidin and its role in iron metabolism is likely to have implications for new therapies for hemochromatosis and anemia of inflammation.

4.1.3. Iron and Immunity

Sufficient iron is known to be important for immune preservation due to its role in promoting the growth of cells of the immune system. However, iron deficiency, as well as its excess, have deleterious effects on the immune status by altering the proliferation and activation of T, B and NK cells. Available cellular iron participates in the modulation of differentiation towards Th1 and Th2 lymphocyte subtypes and their proliferation. A certain amount of metabolically active iron is required by macrophages and neutrophils because iron catalyzes the formation of free hydroxyl radicals directed against invading pathogens and tumor cells. However, an excessive accumulation of iron in immune cells reduces the effectiveness of the effector mechanisms of cellular immunity by reducing the activity of the central cytokine of T cells: interferon y. In short, immune function and iron homeostasis regulate each other. In this way, ACS could be considered an “immune disease”, to the extent that various pathways involved in erythropoiesis are affected by immunological effector molecules and this determines the pathophysiology of ACS.

The Cytokines Involved and Their Effects On Iron Homeostasis Would Be the Following:

− TNF α and IL 1: produce serum hypoferremia and induce ferritin synthesis in macrophages and in the liver. This would increase the deposit of iron in the monocyte-macrophage system, limiting its availability for erythropoiesis.

− IL 1 and IL 6: inhibit the expression of transferrin receptor mRNA.

− They stimulate the synthesis of the divalent metal transporter (DMT-l), which is a transmembrane protein capable of allowing the entry of ferrous iron from the duodenal lumen. IL 6 would induce an increase in hepcidin synthesis, which would affect the intestinal absorption of iron and its release from macrophages

− IFN γ: stimulates the transcription of ferritin, but at the same time inhibits its translation.

− It inhibits the expression of transferrin receptor mRNA, which blocks transferrin receptor-mediated iron incorporation, but increases the expression of DMT-1, thus increasing the entry and retention of ferrous iron.

− It also decreases the mRNA of a transmembrane protein called ferroproteins. Since ferroprotein is responsible for the export of iron from cells, its decrease induced by IFN γ; promotes iron retention within monocytes.

− IL 4, IL 3, and IL 10: Anti-inflammatory cytokines modulate iron homeostasis in activated macrophages.

− Activated murine macrophages, they inhibit the formation of nitric oxide, which increases the translation of ferritin.

− They increase the mRNA of the transferrin receptor, which would tend to reverse the effect of interferon y. In summary, cytokines derived from Th2 cells would be able to increase the incorporation and storage of iron in activated macrophages mediated by the transferrin receptor.

Together, the cytokines derived from Th1 and Th2 lymphocytes would participate in the induction of hypoferremia and hyperferritinemia during the chronic inflammatory process. This would be secondary to divergent effects on:

1. incorporation of iron bound to transferrin, via modulation of transferrin receptor expression

2. the incorporation of ferrous iron, via regulation of the formation of DMT (divalent metal transporter) and hepcidin

3. iron retention, via reduction of ferroproteins expression

4. the export and storage of iron, via induction of ferritin and hepcidin synthesis.

Acute-phase proteins such as alpha 1 antitrypsin and alpha 2 macroglobulin contribute to impaired iron homeostasis by inhibiting transferrin receptor-mediated incorporation into erythroid progenitors.

4.2. Decreased Half-Life of Red Blood Cells

This is a usually moderate decrease (approximately 62 to 90 days, compared to the normal 120 days). It would be secondary to various mechanisms: increased phagocytic activity of macrophages

− RBC membrane damage due to hyperthermia tumor hemolysins or hemolytic bacterial toxins

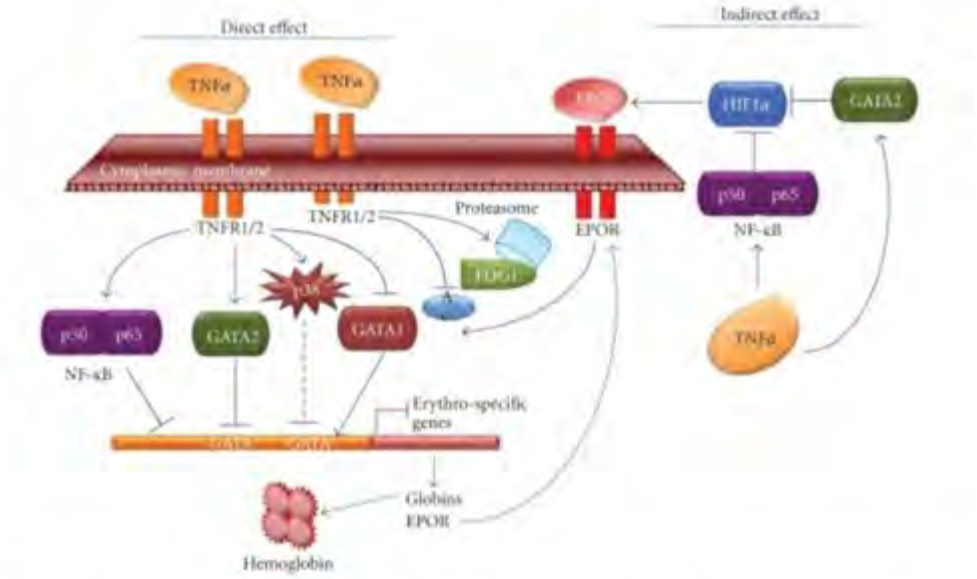
− some degree of mechanical injury to the RBC when traversing damaged tissues

− splenomegaly

Although the evidence in humans is insufficient, there are indications that cytokines could decrease erythrocyte survival and stimulate erythrophagocytosis by macrophages. In vitro, TNF α has been shown to increase phagocytosis of RBCs. To the extent that some patients develop splenomegaly, an increase in erythrophagocytosis and a shortened RBC half-life cannot be ruled out. This explains the increase in GR-derived iron observed in splenic macrophages and Kupffer cells under inflammatory conditions. Hemolysis is infrequent during ACS, but it can contribute to shortening the half-life of RBCs in certain infections such as subacute endocarditis or TB.

4.3. Inhibition of The Proliferation and Differentiation of Erythroid Progenitors

The inhibition of the proliferation and differentiation of erythroid progenitors would be secondary to certain cytokines present in the bone marrow microenvironment, produced by adherent cells of the bone marrow (monocytes and macrophages), which inhibit the growth of erythroid progenitors. TNF α, IFN γ and type 1 interferons block the formation of BFU-E and CFU-E colonies. Of all of them, IFN γ appears to be the most potent inhibitor by directly blocking the proliferation of CFU-E, which explains the inverse relationship between IFN levels and on the one hand and hemoglobin concentration and reticulocyte levels on the other. It has been suggested that the inhibition could depend on a direct inhibitory effect on the formation and/or function of erythropoiesis growth factors such as EPO or could be a consequence of the induction of apoptosis and growth arrest of stem cells. The pro-apoptotic role of TNF on erythroid precursors has been demonstrated in the ACS of rheumatoid arthritis. Graph 1 shows how various cytokines (IFN y, TNF and EPO), regulate the survival and apoptosis of erythroid progenitors (Graph 1), It has been mentioned that the inhibitory effect of IFNy and TNFa would depend in part on their ability to induce the formation of nitric oxide and other free radicals, Finally, the decrease in circulating EPO levels would also play an important role in the inhibition of erythropoiesis, Likewise, the suppression of erythropoiesis can be observed because of the direct invasion of the BM by tumor cells or microorganisms, as well as being secondary to toxic products derived from them, as occurs in HIV infection or malaria.



TNFα inhibits erythropoiesis by direct and indirect effects. In the indirect effect, TNFα activates the transcription factors NF-κB and GATA-2, which were also reported as involved in Epo production inhibition by blocking HIF1α in vitro. Low level of Epo decreases the EpoR-mediated signaling pathways resulting among others, in the down-regulation of GATA-1, and consequently in a possible deregulation of EpoR expression. The direct effect of TNFα via its receptors TNFR1/2 has also been demonstrated. The activation of the NF-κB canonical pathway (p50/p65) inhibits erythro-specific genes expression as globin genes. TNFα was also reported as activating GATA-2 whose over-expression is known to prohibit erythropoiesis in favor of megakaryopoiesis. Conversely, TNFα inhibits GATA-1 in K562, HEL and TF1 cells. GATA-1 expression is affected as well as its acetylation (Ac), and its interaction with FOG1 that was suggested to be degraded by proteasome. Moreover, TNFα was shown to rapidly stimulate p38MAPK phosphorylation in correlation with γ-globin gene down-expression while Epo had a delayed effect on this kinase activation. The combined effects of TNFα result in the decrease in erythro-specific genes expression and hemoglobin production.

Graph 1: TNFα inhibits erythropoiesis by direct and indirect effects.

4.4. Relative Erythropoietin Deficiency

Although the serum levels of EPO are increased, this increase is lower than expected for the degree of anemia of the patient. However, these EPO levels vary according to the underlying disease. 1L 1 AND TNF a decrease EPO secretion. Only 1L 6 would act by stimulating the production of EPO. Likewise, the responsiveness to EPO depends on the severity of the underlying disease and the levels of circulating cytokines, as well as adequate availability of iron for cell proliferation and synthesis of hemoglobin, a condition that is not met in the ACS. The relative deficiency of EPO would be one of the main pathogenic mechanisms of ACS and constitutes the rational basis for the therapeutic use of EPO in these patients.

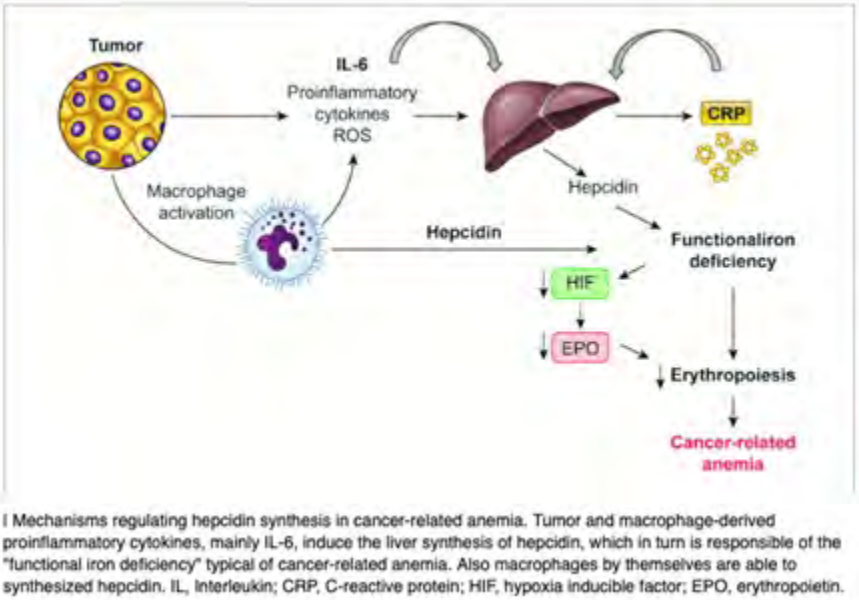
4.5. Other Mechanisms

Other nutritional deficiencies (folates and vitamin B12) could contribute to anemia and poor response to EPO in a subgroup of patients with ACS hospitalized for a long time in intensive care units.

5. Pathophysiology Effects of ACS

For some years now, ACS has been recognized as a syndrome associated with certain inflammatory cytokines, such as interleukins (1L) 1 and 6, turnoral necrosis factor (TNF) and interferons (1FN) α, β and γ. Many of these cytokines are increased in inflammatory, infectious, and neoplastic diseases, and their levels correlate with the degree of disease activity. As previously mentioned, these cytokines would participate in the various pathogenic mechanisms of ACS.

The role of the cytokines mentioned in simple chronic anemia associated with tumor disease is summarized in Graph 2. The development of the ACS could play a beneficial role in the host since it would contribute to the control of the underlying disease. This is since iron is an essential component for all living cells and proliferating organisms. In this way, the alteration of the iron metabolism of the ACS with its disappearance from tumor cells and microorganisms and its accumulation in the monocyte-macrophage system, would limit the availability of this essential nutrient for cells in rapid proliferation and growth. This agrees with the works that mention that the greater availability of iron would be associated with greater risk of tumors, faster progression of turnoral cells or an unfavorable course of infections. The decrease in hemoglobin in ACS would reduce the oxygen transport capacity of the blood, limiting the proliferation of tumor cells and microorganisms. Iron would directly modulate the effectors of the immune system (monocytes and macrophages), and therefore the host's response to the invasion of pathogens and tumor cells.



I Mechanisms regulating hepcidin synthesis in cancer-related anemia. Tumor and macrophage-derived proinflammatory cytokines, mainly IL-6, induce the liver synthesis of hepcidin, which in turn is responsible of the "functional iron deficiency" typical of cancer-related anemia. Also macrophages by themselves are able to synthesized hepcidin. IL, Interleukin; CRP, C-reactive protein; HIF, hypoxia inducible factor; EPO, erythropoietin.

Graph 2: Mechanisms regulating hepcidin synthesis in cancer-related anemia

6. Diagnosis

ACS is the most common anemia in hospitalized patients. It is observed in multiple clinical situations involving chronic inflammatory conditions, such as cancer, chronic infections, or autoimmune diseases. In chronic diseases, various mechanisms that produce anemia are usually associated, such as: iron deficiencies or other nutritional deficiencies, blood loss, hemolysis, renal failure, fibrosis, and marrow infiltration. The diagnosis is simple and is based on the finding of the underlying disturbance of iron metabolism, characterized by the removal of iron from the sites of erythropoiesis and from the circulation, towards the storage sites in the monocyte-macrophage system, which determines the coexistence of hypoferremia with hyperferritininemia. In short, the diagnosis of ACS can be made against a normocytic or microcytic anemia, with decreased serum iron and transferrin saturation, with normal or decreased levels of transferrin and increased iron deposits (measured by the level of ferritin).

Some authors maintain that a ferritin greater than 50 mg/ml excludes the possibility of some component of iron deficiency even in inflammatory states. However, it must be considered that a normal or high ferritin is often difficult to interpret since ferritin is an acute phase reactant protein. Diagnosis of ACS frequently requires a BM examination to rule out tumor infiltration, fibrosis, and infection, exclude myelodysplastic syndromes, and fundamentally carry out an evaluation of iron deposits and their incorporation into erythropoiesis. In this sense, the Perls stain for iron shows in ACS the presence of iron deposits in the monocyte-macrophage system (positive hemosiderin), with negative sideroblasts.

Some algorithms have been developed to diagnose or rule out ACS.

− The combination of ferritin will be less than 70 ng/ml and erythrocyte ferritin less than 4 ag per erythrocyte, it would have a specificity of 0.97 and a positive predictive value of 0.822. LB.

− For patients with rheumatoid arthritis and serological evidence of ACS, certain algorithms are used. A hemoglobin of less than 11 and a serum ferritin of less than 40 in men are considered probable iron deficiency, while if the MCV is greater than 85 and the transferrin saturation is greater than 7%, they are considered carriers of ACS. This formula allows a correct diagnosis in 89% of cases 2.

– More recently, the value of the soluble transferrin receptor in the differential diagnosis between iron deficiency and ACS has been established, so that the association of erythrocyte sedimentation rate, serum ferritin and soluble transferrin receptor would allow differentiation between the two entities. Some authors are somewhat more skeptical about the contribution of the soluble transferrin receptor to the differential diagnosis. The soluble transferrin receptor is a truncated fragment of the membrane receptor that is regulated by the level of intracellular iron available according to the interaction between IRE / IRP. In patients without inflammatory conditions, the level of soluble transferrin receptor is directly related to the need for iron for erythropoiesis. Because soluble transferrin receptor levels are regulated by cytokines, its concentration in the ACS is affected in opposite directions by proinflammatory cytokines and by erythroid iron deficiency. The use of the formula: soluble transferrin receptor/log ferritin has been proposed to differentiate patients with ACS and functional iron deficiency from patients with true iron deficiency. This formula provides an estimate of the iron requirement for erythropoiesis: a low ratio is typical of functional iron deficiency, while a ratio greater than 3 would indicate true iron deficiency in the ACS patient.

There are other parameters that are not necessary for the diagnosis of ACS but can help estimate the iron requirement for erythropoiesis and could have a role in predicting the response of ACS to EPO treatment:

− Zinc-bound protoporphyrin IX: it is formed in erythroid progenitors when the iron availability of these cells is reduced. It increases in the ACS and reflects a demand for iron for erythropoiesis.

− Percentage of hypochromic erythrocytes and reticulocytes.

− Serum EPO level: would have no value for the diagnosis of ACS but would have implications for treatment.

7. Treatment

ACS is generally a moderate, well-tolerated anemia that does not require correction, especially if other contributing factors can be reversed. However, in some cases, ACS can be severe, affecting the functional status and quality of life of patients (example: anemia in cancer patients). In rheumatoid arthritis, the intensity of the anemia correlates with the activity and duration of the disease. The optimal treatment of ACS is the correction of the underlying disease, which is difficult and even impossible in some cases.

Therefore, if the anemia is symptomatic or severe, treatment is required for it.

7.1. Iron Supplement

Generally, the absorption of iron by vein is reduced in ACS, which is why it would be more effective when administered parenterally. However, in patients with ACS secondary to chronic infections or tumors, the administration of iron should only be strictly avoided, in order not to favor the growth and proliferation of microbes and tumor cells and not to alter immune effector mechanisms. In contrast, an iron supplement may be beneficial in patients with ACS secondary to autoimmune diseases or rheumatic diseases. It has been speculated that iron-induced reduction of cellular immunity (by reducing TNF alpha formation) might reduce disease activity and thereby improve ACS by counteracting the activity of TNF α or interferon γ.

7.2. Transfusion

Transfusion therapy is the most common and rapid form of treatment for symptomatic anemia, but it is expensive and potentially dangerous (transmission of infectious diseases, alloimmunization, graft-versus-host disease), and it is a limited resource.

Blood Transfusion Produces Divergent Effects On Immune Function:

− Transfusion of white blood cells, which can circulate in the recipient for more than a year, inducing immunological effects comparable to graft-versus-host disease at a lower level. New transfusion preparation techniques allow depletion of white blood cells to minimize these effects − Blood transfusion induces a state of anergy in the host, secondary to a decrease in Th1 lymphocytes and an increase in Th2.

− It constitutes a very efficient route of iron supply (approximately 200 mg of iron for each unit of 350 to 450 ml), which would have the potentially negative effects described above.

7.3. Recombinant Erythropoietin

The use of EPO was since although its levels are usually high in these patients, the degree of increase is not appropriate for the degree of anemia 16. It was also possible to demonstrate in vitro studies that EPO could reverse the inhibition of erythropoiesis caused by certain cytokines. EPO is more cost-effective than transfusion therapy. It constitutes a therapeutic option in ACS associated with tumors, chronic infections, or autoimmune diseases. The administration of EPO reduces the transfusion requirement and improves the quality of life of these patients. Doses used range from 150 U/kg three times per week to 40,000 U per week. Response rates are sometimes low, which is why a pre-treatment evaluation is recommended to detect the most beneficial patients with this therapy. In patients with ACS associated with rheumatoid arthritis, an EPO dose of 50 to 150 U/kg three times a week allows a six-point increase in hematocrit after at least four weeks of treatment. RA patients who respond to EPO are those with low levels of C-reactive protein.

HIV-positive patients with anemia treated with EPO (especially if endogenous EPO levels are less than 500 VI/l), show a marked decrease in transfusion requirements. Predictors of response to EPO in tumor-associated anemia will be discussed later.

The Mechanisms by Which The EPO Would Act in The ACS Would Be the Following:

− Increased expression of the transferrin receptor in erythroid progenitors by transcriptional and post-transcriptional mechanisms.

− Stimulation of protoporphyrin synthesis which would contribute to iron influx and hemoglobin synthesis.

− Interaction with the activity of cytokines, reducing their antiproliferative effect on erythroid progenitors.

Given the decreased response of erythroid progenitors to EPO, it is likely that more EPO is required to induce a biological response. Being the availability of iron one of the main determinants of the response to EPO, the combination of EPO + iron would have a better response. Despite this, considering the potential risks of the use of iron in ACS associated with tumors or infections, an adequate evaluation of the amount of iron that should be administered is required, so that it contributes to increasing the efficacy of EPO without promoting the growth of tumor cells or impairing immune mechanisms.

8. Anemia of the Cancer Patient

The anemia of the cancer patient deserves some considerations

8.1. Incidence

It constitutes a significant problem, since 20 to 60% of cancer patients develop anemia, which will be of different intensity according to the type of tumor, the nature, and the intensity of the treatment. Approximately 30% of cancer patients receive at least one transfusion during their treatment.

8.2. Prognostic Impact

Anemia in cancer patients worsens their physical and emotional state (producing fatigue, dyspnea, favoring cardiovascular disease and worsening quality of life). It would also have effects on the evolution of patients, by reducing the therapeutic response of those treatments that require optimal oxygen availability, increasing the relapse rate and decreasing survival.

There is much evidence on the prognostic importance of anemia in various types of tumors:

− In a study of 451 patients with stages III and IV of squamous cell cancer of the head and neck, it was possible to demonstrate that pre-treatment hemoglobin levels constituted, in the multivariate analysis, a significant prognostic factor for overall survival and rate of death. 10 co-regional relapse6.

− In a study published in 1998 on 206 patients with ovarian cancer treated with surgery, anemia prior to surgery was an independent factor in the multivariate analysis to predict overall survival.

− Anemia is recognized as a prognostic factor in numerous onco-hematological diseases:

− Chronic myeloid leukemia

− Chronic lymphatic leukemia (CLL)

− Multiple myeloma (MM)

− Hodgkin lymphomas

− Non-Hodgkin lymphomas (NHL)

8.3. Etiopathogenesis

There are numerous factors involved in anemia in cancer patients, such as:

− Hemodilution

− Bleeding

− Hypersplenism, hemophagocytosis

− Kidney failure

− Hemolysis (autoimmune, microangiopathic)

− Nutritional deficiencies (global les, iron, folates, B12)

− BM damage (metastasis, pure red cell aplasia, myelodysplasia)

− Related to the specific treatment

− Chemotherapy (QT): drugs, dose, administration scheme

− Radiotherapy: dose, field, fractionation

− Combined treatments

− Surgery (blood loss)

− Anemia of chronic disorders

Chemotherapy drugs induce anemia through various mechanisms

− Myelosuppression (cyclophosphamide, doxorubicin, etoposide)

− Renal toxicity (cisplatin)

− Immunohemolytic anemia (fludarabine)

− Microangiopathy (hemolytic uremic syndrome)
(Mitomycin C, gemcitabine, oxaliplatin)

Table 2

Chemotherapy-induced anemia has been particularly reported in cisplatin treatments (ovarian cancer, small cell lung tumor), it increases with the number of treatment cycles and the hemoglobin nadir correlates inversely with the cumulative dose platinum.

In 1998, a French group published a proposal for a model to predict anemia and the need for transfusion in patients undergoing chemotherapy.

On a total of 1051 patients (subsequently the study was validated with the inclusion of another 1000 patients), it was possible to determine the factors that in the multivariate analysis showed predictive value for transfusion:

− initial hemoglobin < 12 gr / dl (most significant factor)

− performance status > 1

− Initial lymphocytes < 700 per microliter.

The type of chemotherapy, age, sex and underlying disease did not show significant value.

Baseline hemoglobin <12 was given a value of 3 points, and performance status >1 and lymphocyte count <700 per microliter were given a value of 1 point.

Based on this, a score was created with various probabilities of transfusion, as shown in Table 3 and Graph 3.

Before the use of EPO in the treatment of anemia associated with cancer, transfusion of sedimented RBCs was the only therapeutic resource.

It offers a temporary and short-term increase in Hb levels, being reserved for patients with severe anemia (Hb less than 8 g%), not forgetting the potential risks of transfusion.

Recombinant human erythropoietin has been available since 1989 for the treatment of anemia of renal failure.

There is abundant evidence of the symptomatic benefit and quality of life of EPO in patients with cancers (hematological and solid tumors).

As cancer treatments have improved life expectancy, more emphasis has been placed on quality of life. Fatigue is a very common symptom associated with cancer treatment. Although it is difficult to directly correlate fatigue and other quality of life factors with anemia levels, increasing hemoglobin levels could improve quality of life.

In cancer patients, the response to EPO is observed globally in 140 to 80% of cases, after 4 to 8 weeks of treatment, with differences according to the oncological diagnosis.

The American Society of Clinical Oncology and the American Society of Hematology have published a series of recommendations based on clinical evidence on the use of EPO in anemia associated with tumors, which are listed below:

1. The use of EPO is recommended in patients with anemia associated with CT with hemoglobin (Hb) equal to or less than 10 gr/dl. Transfusions are a therapeutic option depending on the severity of anemia and clinical conditions.

2. For patients with less severe anemia (Hb < 12 but > 10 g/dl), the decision to use EPO immediately or wait for Hb to approach 10 g/dl will depend on clinical conditions. Transfusion in these cases is a therapeutic option.

3. The recommended starting dose is 150 V/kg subcutaneously three times a week for a minimum of 4 weeks. In patients who have not responded to this initial dose, it is recommended that the dose be increased to 300 V/kg three times a week for a further 4 to 8 weeks. Although the evidence is less, an alternative regimen of a weekly dose of 40,000 V can be considered, which can be similarly increased in the absence of response.

4. Patients who after 6 to 8 weeks have not increased Hb levels (at least with an increase of 1 to 2 g), having increased the dose of EPO, will be considered non-responders. Other factors of failure must be ruled out (progression of underlying disease, iron deficiency), and consider stopping EPO treatment.

5. The objective will be to bring the Hb to a level close to 12 gr / dl. At that time, the EPO dose will be decreased, trying to maintain said Hb level. The initial dose of EPO will be restored if the Hb decreases to values close to 10 g/dl. There are not enough data to justify normalizing Hb to values greater than 12 g/dl.

6.Irony, transferrin, transferrin saturation and ferritin values should be monitored at baseline and periodically. Replace iron as needed to minimize EPO requirements. There is still not enough evidence to determine the optimal time and periodicity for such monitoring.

7. There is sufficient evidence for the use of EPO in anemia of low-risk myelodysplastic syndromes. There is insufficient evidence for the use of EPO in anemia of MM, CLL and NHL in the absence of CHT. For patients diagnosed with MM, CLL, NHL, and anemia associated with CT, the above recommendations will be used.

8. In patients with CLL, MM and NHL, treatment with corticosteroids and/or CT will be started first and the hematological response will be observed before considering the use of EPO. If, after starting the oncospecific treatment, no response of anemia is obtained, the use of EPO should be considered following the previous considerations. Blood transfusions are also a therapeutic alternative (Table 4).

Effect of recombinant human erythropoietin (EPO) on transfusion rates and quality of life (QoL) in controlled, randomized studies

A series of factors have been listed that would predict a good response to EPO, such as:

− Low pre-treatment serum EPO concentration (<200 U/litre if Hb is less than 10 gr/dl). A study of 80 patients with various neoplastic diseases identified two important predictors of response to EPO: serum EPO level and serum ferritin concentration. EPO response was less when EPO was >100 mU/mL and/or serum ferritin was >400.

– Hemoglobin value

− Increase in Hb greater than or equal to 0.5 gr / dl after 2 weeks of EPO at less than 100 U/kg.

− Increase in the absolute number of reticulocytes to more than 40,000/ml and increase in Hb equal to> 0.5 gr/dl after two weeks of treatment with EPO.

− Increase in Hb equal to> 0.3 gr / dl AND decrease in basal level of EPO at two weeks. Increase in soluble transferrin receptor equal to or > 25% at two weeks.

Negative response to EPO is predicted by: duration of the neoplasm, treatment of the same, involvement of BM and diagnosis of hematological tumors compared to solid tumors.

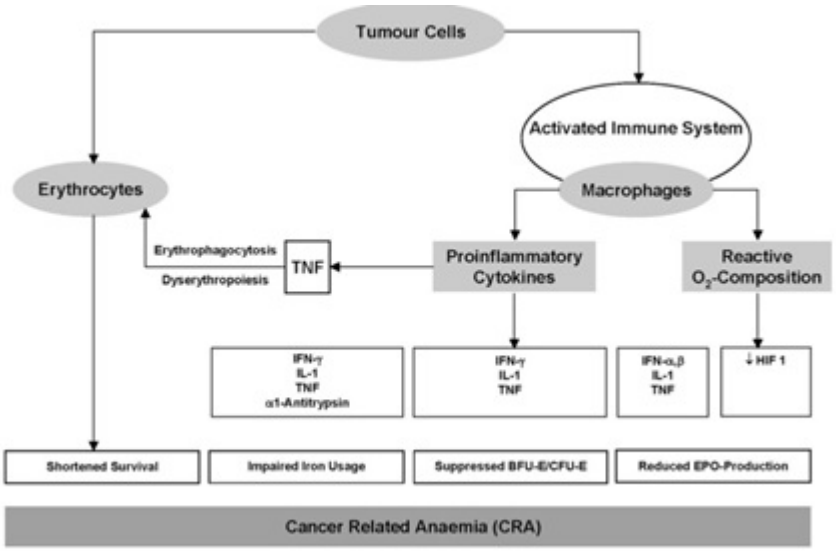
It has been postulated that if after two weeks of treatment with EPO, the serum EPO level is >100 mU/mI and Hb has not increased by at least 0.5 g/dI, or that if after two weeks of treatment, serum ferritin is >400 ng/mL, therapeutic response to EPO is unlikely.

Lastiri et al. recently published their proposed score to predict response to EPO. They treated 36 patients with solid tumors and anemia (hemoglobin < 9.9 g/dI and hematocrit < 30%) with EPO doses of 150 U/kg, 3 times a week, for 12 weeks. They obtained 73.5% of responses with 64% of complete remissions (Hct > 36%).

In this experience, predictors of favorable response were an increase in hemoglobin >0.5 gr/dI at the second week of treatment, CT with cisplatin and pre-treatment serum ferritin >1100 ng/d1. Bone marrow infiltration by tumor was a predictive variable of failure, and pretreatment EPO concentration, early reticulocyte peak at the second week, and pretreatment cytokine dosages (IL 1 and 6, TNF) had no value in predicting response. . Based on this, they developed a predictive score for response to EPO (Table 5). The percentages of complete responses with EPO treatment according to the score and therapeutic recommendation are shown in Table 6.

Table 2: Model to calculate the risk of developing anemia dependent transfusion in patients undergoing chemotherapy

risk of developing anemia	Result	Score Probability of transfusion
− Hb	< 12 g % 3	0 1%
− Functional status	> 1 1	1 4%
– Lymphocytes	< 700 / microliter 1	2-3 11%
		4 30%



Graph 3: Treatment of anemia in cancer patients

Table 3: Correlation between sum and probability of transfusion requirement. To indicate patients with transfusion requirement the cut-off point was set at 3 points

Sum (coefficient)	Probability of transfusion requirement
0	0.2%
2.5	2.9%
3	5%
6	50%
9.5	97%

Table 4: Effect of recombinant human erythropoietin (EPO) on transfusion rates and quality of life (QoL) in controlled, randomized studies

Reference	n	Evaluated	Response control versus EPO (%)	Transfused control versus EPO (%)	QoL rise by EPO
Abels 1992 [27]	413	118[a] 153[b] 132[c]	11 vs 32 14 vs 58 7 vs 48	38 vs 33 49 vs 41[b] 69 vs 53[d]	Sig. Sig. Sig.
Cascinu, 1994 [31]	100	99	2 vs 82	58 vs 20	ND
Osterborg 1996 [31]	155	121	24 vs 60	82 vs 61[e]	ND
Kurz 1997 [32]	35	35	0 vs 57	67 vs 22	NS
Del Mastro 1997 [33]	62	62	ND	6 vs 0	ND
Italian Co-operative Study Group 1998 [41]	87	75	10.8 vs 36.8	ND	ND
ten Bokkel 1998 [34]	122	120	ND	39 vs 4	ND
Thatcher 1999 [35]	130	130	ND	59 vs [33f]	Sig.
Carabantes 1999 [36]	35	35	ND	87 vs 20	Sig.
Oberhoff 1998 [37]	227	189	9 vs 38	41 vs 26	ND
Thompson 2000 [42]	66	66	5 vs 9	90 vs 76	ND
Dammacco 2001 [38]	145	125	9 vs 58	47 vs 27	NS
Littlewood 2001 [39]	375	359	19 vs 71	36 vs 23	Sig.

[a]Without chemotherapy.

[b]With chemotherapy, see also Case et al. [28].

[c]With platinum containing chemotherapy, see also Henry et al. [30].

[d]Over the total study course.

[e]Results from two study arms with different EPO dosages were summarised, first 4 weeks of treatment excluded.

[f]Result from two study arms with different EPO dosages were summarised.

Sig., significant; ND, not determined; NS not significant.

Table 5: Predictive score of response to EPO

1	− Increase in hemoglobin> 0.5 gr / dl at the second week 6
2	− Absence of marrow infiltration 5
3	− Chemotherapy with cisplatin 4
4	− Basal ferritin > 1100 ng/dl 3
5	− Reticulocyte peak at the second week 1
6	− EPO dosage <100 microgs/dl 1

Table 6: Complete response according to predictor score and therapeutic recommendation

Score % of CR Recommendation
0 – 4 0 No EPO
5 – 14 54.5
15 – 20 100 Yes EPO

9. Conclusions and Future Perspectives

− ACS is one of the main causes of anemia in clinical practice, observable in numerous circumstances.

− Frequently coexists with other causes of anemia, which should be investigated, to carry out the optimal treatment of these patients.

− There is multiple clinical evidence on the therapeutic role of recombinant erythropoietin in patients with ACS, especially in rheumatoid arthritis, HIV infection and cancer.

− In this last group of patients, the subgroup of patients potentially most benefiting from treatment with EPO should be adequately defined, to optimize the economic cost of said treatment.

− Knowledge of the intimate physio pathogenic mechanisms will open new therapeutic perspectives in the future, such as the innovative clinical use of monoclonal antibodies against TNF, which have begun to be used in patients with rheumatoid arthritis with promising results.

References

1. Cartwrigt GE. The anemia of emonic diseases. Semin Hematol. 1966; 3: 351.
2. Garrdner L, Benz E. In Hematology. Basic Principles and Practice. Hoffman, 3rd edition, Churchill Livingstone, 2000.
3. Cash JM, Sears DA. The anemia of chromc disease: spectrum of associated diseases in a series of unselected hospitalized patients. Am J Med. 1989; 87: 638-44.
4. Feelders RA, Vreugdenhil G, van Dijk J. Decreased affinity and number of transferring receptors on erythmoblasts in the anemia of rheumatoid arthritis. Am. J. Hematol. 1993; 43: 200-4.
5. Lee GR. The anemia of cmome disease. Semin Hematol. 1983; 20: 61.
6. Weiss G. Pathogenesis and treatment of anemia of chronic disease. Blood Reviews. 2002; 16: 87-96.
7. Ganz T. Hepcidin, a key regulator of iron metabolism and mediator of anemia of inflammation. Blood. 2003; 102: 783-8.
8. Robson KJ. Hepcidin and its role in iron absorption. Gut. 2004; 53 :617-19.
9. Nemeth E, Rivera E, Gabayan V. IL-6 mediates hypoferremia of inflammation by inducing the synthesis of the iron regulatory hormone hepcidin. J Clin Invest. 2004; 113: 1271-6.
10. Beutler E. Unlocking the mysteries of iron homeostasis and of the anemia of chronic disease: is hepcidin the key? Blood. 2003; 102, 775.
11. Nourousian M. Pathophysiology of anemia. Anemia and Cancer Therapy ESSO. Milan, November 2001.
12. Means RT, Krantz SB. Progress in understanding the pathogenesis of the anemia of chronic disease. Blood.1992; 80: 1639-47.
13. Faquin WC, Schneider TJ, Goldberg MA. Effect of inflammatory etokines on hypoxia-indueed erythropoietin production. Bloom. 1992; 79:1987-94.
14. Salleri C, Maciejewski JP, Sato T, Young NS. Interferon-gamma eonstitutively expressed in the stromal microenvironment of human marrow cultures mediates potent hematopoietic inhibition. Bloom.1996; 87: 4149-57.
15. Papadaki HA, Kritikos HD, Valatas V. Anemia of chronic disease in rheumatoid arthritis is associated with increased apoptosis of bone marrow erythroid cells: improvement following anti-tumor necrosis factor alpha antibody therapy. Blood.2002; 100: 474-82.
16. Miller CB, Jones RJ, Piantadosi S. Decreased erythropoietin response in patients with the anemia of cancer. N Eng J Med. 1990; 322: 1689-92.
17. Means RT Jr, Krantz SB. Inhibition of human erythroid colony-forming units by gamma interferon can be correctd by recombinant human erythropoietin. Blood. 1991; 78: 2564-7.
18. Balaban EP, Sheehan RG, Demian SE. Evaluation of bone marrow iron stores in anemia associated with chronic disease: a comparative study of serum and red cel! ferritin. Am J Hematol. 1993; 42: 177-81.
19. Punnone K, Irjala K, Rajamaki A. Serum transferrin receptor and its ratio to serum ferritin in the diagnosis of iron deficiency. Blood. 1997; 89: 1052-7.
20. Hastka J, Lasserre J, Schwarzbeck A, Strauch M, Hehlmann R. Zinc protoporphyrin in anemia of chronic disorders. Blood. 1993; 81: 1200-4.
21. Cremieux PY, Finkelstein SN, Berndt ER. Cost effectiveness, quality-adjusted life years and supportive careo Pharmacoeconomics. 1999; 16459.
22. Skillings JR, Sridhar FG, Wong C. The frequency of red cell transfusion for anemia in patients receiving chemotherapy. Am J Clin Oncol.1993; 16: 22-5.
23. Dalton JD, Bailey NP, Barett-Lee PJ. Multicenter UK audit of anemia in patients receiving cytotoxic chemotherapy. Proc Am Soc Clin Oncol 1998; 17: 418.
24. Groopman JE, Itri LM. Chemotherapy-induced anemia in adults: Incidence and treatment. J Natl Cancer Inst 1999; 91: 1616-34.
25. Cella D, Kallich J, McDermott A, Xu X. The longitudinal relationship of hemoglobin, fatigue and quality of life in anemic cancer patients: results from five randomized clinical trials. Ann Oncol 2004; 15: 979-86.

26. Ludwig H, Fritz E. Anemia in cancer patients. Semin Oncol. 1998; 25: 2-6.
27. Sazama K. Reports of 355 transfusion-associated deaths: 1976 through 1985. Transfusion. 1990; 30: 583-90.
28. Engert A. Recombinant human erythropoietin as an alternative to blood transfusion in cancer-related anaemia. Dis Manage Health Outcomes. 2000; 8: 259-72.
29. Nowrousian MR. Recombinant human erythropoietin in the treatment of cancer-related or chemotherapy-induced anaemia in patients with solid tumours. Med Oncol 1998; 15 (Suppl 1): 19–28.
30. Rizzo JD, Lichtin AE, Woolf SH et al. Use of epoetin in patients with cancer: Evidence-based clinical practice guidelines of the American Society of Clinical Oncology and the American Society of Hematology. J Clin Oncol 2002; 19: 4083–107.
31. Bokemeyer C, Aapro MS, Courdi A et al. EORTC guidelines for the use of erythropoietic proteins in anaemic patients with cancer. Eur J Cancer 2004; 40: 2201–2216.
32. Egrie JC, Browne JK. Development and characterization of darbepoetin alfa. Oncology 2002; 16 (Suppl): 13–22.
33. Lai PH, Everett R, Wang FF et al. Structural characterisation of human erythropoietin. J Biochem Chem 1986; 261: 3116–21.
34. Dordal MS, Wang FF, Goldwasser E. The role of carbohydrate in erythropoietin action. Endocrinology 1985; 116: 2293–9.
35. Goldwasser E, Kung CK, Eliason J. On the mechanism of erythropoi- etin induced differentiation. 13. The role of sialic acid in erythropoietin action. J Biol Chem 1974; 249: 4202–6.
36. Faulds D, Sorkin EM. Epoetin (recombinant human erythropoietin). A review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential in anaemia and the stimulation of erythropoiesis. Drugs 1989; 38: 863–99.
37. Miller CB, Jones RJ, Piantadosi S et al. Decreased erythropoietin re- sponse in patients with the anemia of cancer. N Engl J Med 1990; 322: 1689–92.
38. Spivak JL. Cancer related anemia: Its causes and characteristics. Semin Oncol 1994; 21: 3–8.
39. Nowrousian MR, Kasper C, Oberhoff C et al. Rh-Erythropoietin in cancer supportive treatment. New York: Marcel Dekker 1996.
40. Nowrousian MR. Recombinant human erythropoietin in the treatment of cancer-related or chemotherapy-induced anaemia in patients with solid tumours. Med Oncol 1998; 15 (Suppl 1): 19–28.
41. Ludwig H, Strasser K. Symptomatology of anemia. Semin Oncol 2001; (Suppl 8): 7–14.
42. Pawlicki M, Jassem J, Bosze P et al. Multicenter study of recombinant human erythropoietin (epoetin alpha) in the management of anemia in cancer patients receiving chemotherapy. Anticancer Drugs 1997; 8: 949–57.
43. Vogelzang NJ, Breitbart W, Cella D et al. Patient, caregiver, and oncologist perceptions of cancer-related fatigue: Results of a tripart assessment survey. Semin Hematol 1997; 34 (Suppl 2): 4–12.
44. Ortho Biotech, Inc. Package Insert 2003.
45. Hoffmann-La Roche Ltd. Package Insert 2004.
46. Amgen Inc. Package Insert 2003.
47. Egrie JC, Dwyer E, Browne JK et al. Darbepoetin alfa has a longer circulating half-life and greater in vivo potency than recombinant human erythropoietin. Exp Hematol 2003; 31: 290–9.
48. Abels RI. Recombinant human erythropoietin in the treatment of the anaemia of cancer. Acta Haematol 1992; 87 (Suppl 1): 4–11.
49. Abels RI. Recombinant human erythropoietin in the treatment of the anaemia of cancer. Acta Haematol. 1992; 87: 4-11.
50. Case DC, Bukowski RM, Carey RW. Recombinant human erythropoietin therapy for anemic cancer patients on combination chemo - therapy. Natl Cancer Inst. 1993; 85: 801-6.
51. Cascinu S, Fedeli A, Del Ferro E. Recombinant human erythropoietin treatment in cisplatin-associated anemia: a ran- domized, double-blind trial with placebo. J Clin Oncol. 1994; 12: 1058-62.
52. Henry DH, Brooks BJ, Case DC. Recombinant human erythro- poietin therapy for anemic cancer patients receiving cisplatin chemotherapy. Cancer J Sci Am. 1995; 1: 252-60.
53. Rizzo JD, Lichtin AE, Woolf SH. Use of epoetin in patients with cancer: Evidence-based clinical practice guidelines of the American Society of Clinical Oncology and the American Society of Hematology. J Clin Oncol. 2002; 19: 4083-107.