ASSESSMENT AND DIAGNOSIS OF ANEMIA

APPENDIX: CANCER-RELATED ANEMIA

By

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ASSESSMENT AND DIAGNOSIS OF
ANEMIA

Abstract

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Washington State University
May 2000

Chair: Renee Hoeksel,

Anemia is the most common hematologic problem and occurs across the human lifespan, in otherwise healthy as well as critically ill patients. This paper addresses the clinical and laboratory assessments of patients presenting with anemia, and outlines the differential diagnoses of the cause of anemia. The appendix presents a review of anemia in the cancer patients, the prevalence of fatigue in cancer-related anemia, and the impact of fatigue on the quality of life. Finally, the advance of erythropoietin treatment for chronic anemia is evaluated, along with its potential for improvement of the quality of life.
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Introduction

Anemia has been defined as a reduction in either the red blood cell volume or the concentration of hemoglobin in the blood, resulting in a decrease in the oxygen-carrying capacity of the blood. Anemia is the most common hematologic problem and occurs across the human lifespan in otherwise healthy, as well as critically ill patients (Lynch & Jacobs, 1997). This paper addresses the clinical and laboratory assessments of patients presenting with anemia, and outlines the differential diagnoses of the causes of anemia.

From a laboratory standpoint, the presence and severity of anemia are easily described based on the deviation of the patient’s hemoglobin/hematocrit from the standard normal values shown in Table 1. However, from a clinical perspective the diagnosis of anemia is more complex. Measurements of red blood cell production, maturation, morphology, and iron supply are used to identify and classify an anemia as a defect of either marrow production, erythroid precursor maturation, or adult red blood cell survival (Hillman, 1998).

Epidemiology

The most common cause of anemia in the United States is due to iron deficiency (Ansell, 1996). Iron deficiency results in a maturation abnormality with decreased hemoglobin and red cell production and represents one quarter of the anemias seen in hospitalized patients. Anemia caused by acute blood loss represents another 25% of anemia cases in hospitalized patients and anemia caused by certain chronic inflammatory diseases, represent a further 25%. The remaining 25% of patients suffer from all other causes of anemia. For non-hospital-based patients, the first three categories probably account for 90% of cases of anemia seen by practitioners in the office setting (Ansell, 1996).
Anemia is common in the elderly; 2.3% of men and 5.5% of women over age 65 have a hemoglobin level less than 12 g/dl (Devereaux-Melillo, 1993). On routine screening, as many as 10-23% of elderly patients will have low vitamin B12 levels, directly linked to pernicious anemia (Deloughery, 1999). Finally, anemia is a common effect of cancer and its treatment, with nearly 90% of cancer patients presenting with anemia during the course of their disease (Casadevall, 1998).

**Etiologies**

Anemia is considered a symptom, not a disease itself (DeLoughery, 1999). Anemia can result from a decrease in red cell production or an increase in peripheral destruction of mature red cells. Production defects can be of nutritional origin, resulting from deficiencies in vitamin B12, folate or iron. Or, it can be related to an inflammatory process or chronic disease. Finally, it could be secondary to marrow disorders leading to pure red cell aplasia. Abnormal peripheral destruction of mature red cells that is not adequately compensated by increased production can be seen in massive or chronic blood loss or increased cell destruction such as hemolytic anemia. Finally, signs of anemia can also be attributed to blood sequestration resulting from hypersplenism or increased plasma volume (dilutional effect) primarily seen in pregnancy, lactation or in the hospitalized patient.

**The Red Blood Cell Physiology**

The circulating red blood cell (RBC) is little more than a container for hemoglobin, specializing in oxygen transport and delivery. Red blood cells transport oxygen from the lungs to the tissues and carry carbon dioxide back from the tissues to the lungs. Since hemoglobin is necessary to
transport oxygen, the physiologic result of anemia is tissue hypoxia, which can affect every organ system (Lynch & Jacobs, 1998). If anemia has a slow onset, adaptations to increase oxygen maintenance occur, such as increase of plasma volume and right shift of the oxygen-hemoglobin dissociation curve. If anemia develops rapidly there may not be adequate time for compensatory adjustments to occur, leading to a sudden marked contraction of intravascular volume, resulting in postural hypotension, fall in cardiac output, and shunting of blood from skin to central organs (Hillman, 1998).

Because the RBC lacks a nucleus and mitochondria, it has barely enough metabolic reserve to sustain a four-month life span in the peripheral circulation. Under normal conditions, the total red cell mass is maintained within narrow limits by the regulatory hormone erythropoietin. Red blood cells originate in the bone marrow as undifferentiated stem cells. The stem cell is differentiated into a red blood cell when decreased oxygen tension at the kidney initiates the erythropoietin feedback system (Figure 1). When tissue oxygenation is low, erythropoietin levels increase and stimulate red cell production. When tissue oxygenation is adequate, erythropoietin levels are low and red cell production is decreased. Healthy bone marrow has a tremendous capacity to adjust cell production to meet the body’s needs (Hillman, 1998).

Reticulocytes can be thought of as “adolescent” red blood cells (Lynch & Jacobs, 1998). Reticulocytes have reached the last stage of erythropoiesis in the bone marrow and are released into the peripheral blood. A reticulocyte circulates in the bloodstream for twenty-four hours before maturing into a RBC. Reticulocyte counts are therefore, a good indicator of bone marrow activity.
Clinical Presentation

A detailed history and physical examination are essential to the diagnosis and evaluation of anemia. Racial background and family history of anemia are valuable, since many of the red blood cell metabolic defects follow ethnic lines and are hereditary (Hillman, 1998). History of acute or chronic illness, history of blood loss (including history of menses), past blood counts and history of blood transfusion, nutritional habits, drug or alcohol habits, need to be carefully evaluated. Clinical presentation of the patient with anemia can be insidious. The clinical manifestation of anemia varies with age, degree and rapidity of onset, presence of underlying illness and other factors. A mild anemia is often asymptomatic. When symptoms do develop, patients will report increased fatigue, dyspnea, headache, lightheadedness, palpitations, anorexia, and occasionally syncope. Patients may also report blood in feces and vomit. Women commonly develop abnormal menstruation, manifested as amenorrhea or increased bleeding. Men can develop a decrease in libido and impotence (DeLoughery, 1999). In older people, angina pectoris can be an important clinical manifestation of anemia (Howard & Hamilton, 1997). Physical findings can include pallor (color of skin, palms, oral and conjunctival mucous membrane and nail beds), jaundice, tachycardia, ejection systolic murmur, mild peripheral edema, petechiae, leg ulcers, and hepatoplenomegaly (Chapman, 1996).

Laboratory Assessment

The basic laboratory exams for assessment and classification of anemia include a complete blood count (CBC), and a reticulocyte count. The CBC includes hemoglobin, hematocrit and red cell indices. Normal values are age and sex dependent. Table 1 lists the
normal values for the common laboratory tests used in evaluating anemia. A complete metabolic panel is valuable at this point of the anemia work-up to evaluate for kidney failure, liver disease, or endocrine problems that could contribute to anemia.

The next level of testing is more specific to further explain the etiology of the anemia. The tests include iron studies (serum iron, ferritin level, total iron binding capacity and iron saturation), erythropoietin level, vitamin B12, folate, and Coomb’s test.

Given the frequency of iron deficiency anemia, serum ferritin should be checked in all anemic patients. Serum ferritin is directly correlated with total body iron stores, with 1 mcg/L serum ferritin representing 8-10 mg of stored iron. A ferritin level of less than 10 mcg/L has 60-75% sensitivity for iron deficiency anemia (Nicoll, McPhee, Chou, & Detmer, 1997). Conversely, ferritin greater than 100 mcg/L, rules out iron deficiency anemia in most patient. Ferritin levels can be falsely elevated in acute hepatitis or liver necrosis, disseminated tuberculosis and Hodgkin’s disease. The high specificity and moderate sensitivity of the serum ferritin makes it the most useful and cost-effective test of iron stores (DeLoughery, 1999).

Serum iron testing, on the other hand, is lacking in both specificity and sensitivity. Iron levels can be decreased in a variety of physiological states including iron deficiency, inflammation, and stress. The serum iron level varies tremendously from morning to evening and from day to day. The minuscule amount of iron in a multivitamin can falsely elevate the serum iron for up to 24 hours (DeLoughery, 1999). The total iron binding capacity is very specific for iron deficiency (near 100%), but has poor sensitivity (less than 30%) (DeLoughery, 1999). The iron saturation (Fe/TIBC x 100) can be decreased below 16% in both anemia of chronic disease and iron deficiency and is of little help distinguishing between the two diagnosis (DeLoughery, 1999).
Erythropoietin (EPO) levels fluctuate with arterial content of oxygen. There is also a diurnal variation where serum EPO is higher in the morning than in the evening. In renal insufficiency, a progressive anemia develops when creatinine clearance falls below 50 ml/min with a rough correlation between the severity of anemia and the degree of renal impairment. Anemia in renal failure results from a relative decrease in erythropoietin production. In anemia of chronic disease, an inappropriately low serum erythropoietin level is found for a given level of anemia (Burd, 1998) giving it poor reliability and validity in these patients.

Vitamin B12 and folic acid are both dependent on a normally functioning intestinal mucosa for their absorption and are important for the production of red blood cells. In most cases, the underlying cause of folic deficiency can be determined by the patient’s history. If malabsorption is suspected, then both serum B12 and folate levels should be measured. However, B12 levels are neither specific nor sensitive for B12 deficiency. As many as 30% of patients, with neurological disease due to vitamin B12 deficiency will have no hematological symptoms. Recently, there has been interest in measuring levels of serum homocysteine and methylmalonic acids. These precursors build up in B12 deficiency and are more accurate indicators of tissue B12 deficiency (DeLoughery, 1999).

Coomb’s test detects immunoglobulin antibodies or complement on the red cell membrane (Lynch & Jacobs, 1997). A positive direct Coomb’s test is significant for autoimmune hemolytic anemia or transfusion reaction. The test has relatively high specificity with false negative tests, occurring in 2-5% of patients with immune hemolytic anemia (DeLoughery, 1999).

Bone marrow sampling is of greatest value for patients who have hypoproliferative anemia or a disorder of red blood cell maturation. The examination of bone marrow smears provides valuable information as to the marrow structure and cellularity, as well as to the proliferation and
maturation of blood cell precursors. Indications for bone marrow biopsy are: pancytopenia, unexplained anemia, anemia with very low reticulocyte count (<0.1%), blood smear with immature white and red cells, blood smear suggestive of myelodysplasia or of leukemia (DeLoughery, 1999).

**Diagnostic Approach**

The evaluation of a patient with a decreased hematocrit (as depicted in Figure 2) includes a careful review of the history and physical findings, exclusion of acute blood loss, and evaluation of hydration status. Presence of pancytopenia requires a bone marrow examination. The next step is to determine whether the anemia results from decreased production or increased destruction of red blood cells. The reticulocyte count is critical and must be adjusted for the patient’s hematocrit (See Table 2). A second correction is necessary when intense erythropoietin stimulation results in early release of reticulocytes from bone marrow. These “stress reticulocytes” will survive an extra 24-48 hours in the circulation and will inflate the estimation of RBC production if a maturation correction is not applied (See Table 2).

Morphologic evaluation of the blood smear, and evaluation of the Mean Corpuscular Volume (MCV) allow for a differentiation between microcytic, normocytic and macrocytic anemia (See Table 3.). With microcytic cells, iron studies are indicated to differentiate between iron deficiency and anemia of chronic disease (ACD), or thalassemias. Low serum iron, high Total Iron Binding Capacity (TIBC), and low ferritin are indicative of an iron deficiency anemia, while low serum iron, low TIBC, and high ferritin are highly suggestive of ACD (DeLoughery, 1999). If the iron studies are normal and there is marked poikilocytosis, and target cell formation is apparent on the blood smear, then hemoglobin electrophoresis should be done to evaluated for
Thalassemia. If these studies are within normal ranges, a bone marrow biopsy is indicated to look for sideroblastic anemia or preleukemic states (DeLoughery, 1999).

Normocytic cells with low ferritin level could indicate an early stage of iron deficiency anemia. In normocytic anemia, assessment of renal function and an erythropoietin level are indicated, to rule out anemia of renal disease. Normal renal function and a normal ferritin level in the presence of normocytic anemia and with no evidence of endocrine or inflammatory diseases, indicates the need for a bone marrow aspiration and biopsy to exclude pure red cell aplasia or refractory anemia (Hillman, 1998).

With the presence of macrocytic cells, an evaluation of vitamin B12 and red cell folate is indicated to rule out megaloblastic anemia. If vitamin B12 and folate are normal, an evaluation of liver functions is warranted to rule out liver disease. At this point, absence of a diagnosis would require a bone marrow biopsy.

An increase in absolute reticulocytes (greater than 2-3%) is seen in blood loss and acute hemolytic processes. Occult blood loss must be ruled out. Elevated bilirubin and lactate dehydrogenase are indicative of RBC destruction. Evidence of red cell fragmentation on the blood smear could be the result of mechanical destruction either by a prosthetic valve or by disseminated intravascular coagulation. If sickle cells are present on the peripheral blood smear, hemoglobin electrophoresis is indicated to rule out sickle cell anemia (Chapman, 1996). Autoimmune hemolytic anemia would be identified by a positive indirect Coomb’s test. Other causes of increased destruction of red cells include paroxysmal nocturnal hemoglobinuria, for which a positive urinary homocysteine is diagnostic. Enzyme deficiencies may also affect survival of red blood cells. The most common is glucose-6-phosphate dehydrogenase deficiency, which is gender linked and thus only affects males (DeLoughery, 1999).
Cost Analysis for Diagnostic Approach

The initial diagnostic approach for anemia is relatively inexpensive. A complete blood count (CBC) and chemistry panels are routine laboratory tests. Results are available within two hours after a standard blood draw and no special patient preparation is needed. The reticulocyte count can be added to the CBC without extra intervention, at little cost and with no delay for results. At this point, the clinician has enough data to confirm anemia, rule out pancytopenia, and differentiate maturation disorders from increased red cell destruction. A careful review of the peripheral blood smear will confirm the diagnostic differential and further guide the diagnosis based on red cell morphology. If a maturation disorder is suspected, a ferritin level should be done early in the diagnostic process because of the high incidence of iron deficiency anemia. Ferritin level is considered the most useful and cost-effective test of iron stores and it is obtained from a simple blood draw with no special patient preparation and results are reported quickly. A ferritin level below normal strongly suggests iron deficiency anemia. A positive response to treatment with iron supplementation would confirm this diagnosis. Additional iron studies such as serum iron level, TIBC and iron saturation are not specific enough to add useful information to the diagnosis and add unnecessary costs. However, it is important to keep in mind that if there is an index of suspicion for ACD, these additional iron studies will help differentiate the etiology of the microcytic anemia.

A careful assessment of the chemistry panel (BUN, creatinine) will guide the clinician further down the algorithm to rule out anemia secondary to kidney failure. Increased liver function could suggest hemolysis. More tests may be required such as erythropoietin level, vitamin B12, folate, and serum homocysteine. These tests are not routine, but are easily obtained from a simple blood draw, with no special patient preparation. The results may not be available
for 12 to 24 hours and the cost is significant. Coomb’s antiglobulin and hemoglobin electrophoresis are more sophisticated requiring more time and expense but can be performed from a simple blood draw with no special patient preparation.

Bone marrow aspiration with biopsy should be kept as the test of last resort. It is the most expensive test and involves significant risks and pain for the patient. Risks of infection and hemorrhage must be considered and included in the consent discussion. The procedure is painful, and conscious sedation with close monitoring is required. Preliminary results may be available within a few days, but the final pathology report can take up to 2 weeks.

**Selected Type of Anemias**

**Iron deficiency.**

Iron deficiency is the most frequent cause of anemia. It results from inadequate absorption, or excessive loss of iron. Iron is essential in hemoglobin synthesis, DNA synthesis, and other vital enzymatic reactions. Iron deficiency most frequently occurs in young children, in women during reproductive years, and in the elderly. In adults, iron deficiency is rarely due to inadequate nutritional intake. Intestinal malabsorption of iron is an uncommon cause of iron deficiency, except in malabsorption syndromes or after gastrointestinal surgery. Chronic blood loss is the most common cause of iron deficiency. In non-menopausal women, iron deficiency is commonly due to unreplaced iron losses from menstruation or repeated pregnancies. When bleeding is occult, it is usually of gastrointestinal origin from peptic ulcers, gastritis, polyps, or tumors (Chapman, 1996).

Symptoms of iron deficiency include paresthesias, brittle nails, sore tongue, and pica (the desire to eat unusual substances, often of little nutritional value, such as starch, ice, or clay). On
physical examination, these patients may have pallor, glossitis, papillary atrophy of the tongue, and rarely spoon nails (Fairbanks, 1995). A low serum ferritin level, less than 10 mcg/L, is generally considered diagnostic of iron deficiency and values less than 20 mcg/L are suggestive of an iron deficient state. However, a plasma ferritin in the normal range does not necessarily rule out iron deficiency (Miller, 1997). As an alternative diagnostic path, a general practitioner may choose to evaluate the status of the patient’s iron stores with a therapeutic trial of oral iron supplements (325 mg of ferrous sulfate three times a day for 2 months). A positive response would confirm the diagnosis of iron deficiency anemia (Howard & Hamilton, 1997).

**Anemia of chronic disease**

Patients with anemia of chronic disease usually present with mild to moderate anemia. Laboratory studies reveal that hemoglobin is rarely less than 8 gm/dl and MCV is low to normal. Serum iron level and iron-binding capacity are low, with a normal or elevated ferritin level (DeLoughery, 1999). ACD is associated with infectious, inflammatory, malignant, and connective tissue disorders lasting more than a few weeks. ACD may be found in combination with iron deficiency. At least three factors are implicated in the pathology of ACD. The first is a shortened life span of the red blood cell from 120 days, down to 60-90 days secondary to enhanced phagocytic activity by macrophages or hemolysis caused by bacterial toxins or tumor secretions. Fever may also contribute to this shortened survival by damaging the red blood cell cytoskeleton. The second factor in the pathogenesis of ACD is altered iron metabolism resulting in a defect in the transfer of iron from bone marrow stores to the plasma. Two proteins have been implicated in this metabolic alteration, lactoferrin and apoferritin. Lactoferrin competes with transferrin and binds to iron preventing transport to the plasma. Apoferritin is produced in
excess in malignant and inflammatory conditions. It binds with a greater than usual amount of iron, leaving very little iron for transfer to plasma. The third factor in ACD pathogenesis is an impaired bone marrow response to the anemia. The normal response of the body to decreased oxygen-carrying capacity is to increase the production of erythropoietin. This hormone, produced by the kidneys, can accelerate the production of erythrocytes. It works by stimulating red blood cell precursors in the marrow to speed maturation and subsequent release of the red blood cells into the circulation. In ACD, there is either a deficiency of erythropoietin or it is appropriately increased, but the bone marrow response is blunted. Under normal circumstances, the bone marrow is able to compensate and increase production of erythrocytes, but in ACD this does not happen (Richer, 1997).

**Megaloblastic Anemias**

Megaloblastic anemias occur when a folate or vitamin B12 deficiency (pernicious anemia) causes aberrant DNA synthesis. Megalocytic anemias are macrocytic, hyperchromic and present with decreased reticulocyte counts. The hematologic picture is identical in vitamin B12 and folate deficiency, but patients exhibit different physical findings. Deficient B12 and folate levels confirm the diagnosis (Hines, 1995).

The most common causes of vitamin B12 deficiency are lack of intrinsic factor, intrinsic factor inhibition, small intestine disorders, gastric surgery, pregnancy, intestinal tapeworm, and hyperthyroidism. Vitamin B12 deficiency develops insidiously and is often associated with progressive complaints of fatigue, weakness, and paresthesias. Physical examination reveals glossitis, decreased vibratory sensation and proprioception, ataxia, and spastic weakness. If not corrected, impairment of the peripheral nerves can progress to spinal cord involvement.
Treatment consists of weekly injections for initial repletion, followed by monthly lifelong maintenance therapy (Lynch & Jacob, 1997).

Folate deficiency can develop in just a few months after inadequate intake. The most common causes are insufficient dietary intake and overcooking of food. Other causes include alcoholism, malabsorption, and ingestion of folic acid antagonists such as anticonvulsants, oral contraceptives, triamterene, sulfasalazine, and trimethoprim/sulfamethoxazole. The clinical findings of folate deficiency are similar to vitamin B12 deficiency, except for the absence of neurologic symptoms. Deficiency is treated with oral folate repletion of 1 mg daily. Duration of treatment depends on the cause of the deficiency (Lynch & Jacob, 1997).

Thalassemias

The alpha and beta-thalassemias are inherited autosomal recessive disorders characterized by abnormal hemoglobin synthesis. Beta-thalassemia is most prevalent among persons of Mediterranean origin. Alpha-thalassemia, in which the alpha chain is affected, is most common among populations of Southeast Asia. Both alpha and beta-thalassemia are common among African-Americans. Alpha and beta thalassemia can be major or minor, depending on how many genes are defective and whether the defects are inherited homozygously (major) or heterozygously (minor). Thalassemia major (rare) causes severe and often fatal anemia in infancy. Thalassemia minor is a mild, often asymptomatic anemia and is more frequently encountered in clinical practice.

The anemic manifestation of thalassemia is microcytic-hypochromic hemolytic anemia. Usually the reticulocyte count is elevated or normal with normal iron and ferritin levels. The
diagnosis is confirmed by a hemoglobin electrophoresis that shows elevated hemoglobin A2 or F instead of the normal hemoglobin A (Burd, 1998; Lynch & Jacobs, 1997).

**Hemolytic anemia**

Hemolytic anemias are a group of disorders in which red blood cell survival is reduced, either episodically or continuously. Hemolytic disorders are due to primary abnormalities of the RBC (inherited) or abnormalities in the RBC environment (acquired). They are classified as intrinsic or extrinsic hemolysis, according to the primary site of RBC destruction (Linker, 1997). Intrinsic hemolytic anemias result from RBC membrane defects, enzyme deficiencies (G6PD), or defects in the actual RBCs caused by abnormal hemoglobin (e.g. sickle cell anemia). In extrinsic hemolytic anemias, normal RBCs are prematurely destroyed by trapping within the liver or spleen, antibody-mediated action, infections, drug toxicity, or mechanical injury as seen in thrombotic thrombocytopenia purpura, hemolytic-uremic syndrome, disseminated intravascular coagulation, or valve hemolysis (Worrall, Tompkins & Rust, 1999).

Certain laboratory features are common to all the hemolytic anemias. They include reticulocytosis with either falling or stable hematocrit, elevated Lactate Dehydrogenase (LDH), and increased indirect bilirubin. Blood smear examination is particularly useful in assessment of hemolytic anemias as identification of specific poikilocytes may lead to a diagnosis. Plasma hemoglobin, urine hemoglobin and urine hemosiderin are found in cases of intravascular hemolysis and serve to distinguish intravascular from extravascular destruction of RBC’s (Lynch & Jacobs, 1997)
Management of Anemia

Patients with symptomatic, but transient anemia resulting from acute blood loss or those with symptomatic chronic anemia should receive crystalloids to replace intravascular volume, followed by red blood cell transfusion as soon as available (Koeller, 1998). Patients with euvoletic, but symptomatic anemia should also be transfused with red blood cells to relieve the symptoms. Iron, folate, or vitamin B12 deficiencies should be assessed and corrected with the appropriate replacement therapy (Koeller, 1998).

RBC transfusions, while ameliorating anemia, are associated with risks, the most serious of which is potential transmission of infectious diseases. Although the blood supply is now carefully screened and the risk of human immunodeficiency virus (HIV) transmission is negligible, infectious agents, such as the hepatitis viruses, cytomegalovirus, Epstein-Barr virus, and exotic microbes remain a concern (Goodnough, Brecher, Kanter, & AuBuchon, 1999; Rieger, 1995). Other serious adverse events associated with allogenic transfusion include alloimmunization, allergic reactions, hemolytic reactions, iron and circulatory overload, and immunosuppressive effects (Groopman & Itri, 1999). Other issues to consider include the cost of transfusion therapy as well as the limited blood supply.

With the advent of recombinant human erythropoietin (Epoetin alfa from Amgen Inc. & Procrit from Ortho Biotech Inc.), drug therapy is now available that can decrease and potentially alleviate the need for transfusion in chronic anemia. Although erythropoietin treatment has been successfully used for the anemia of renal failure, its application for other types of anemia is a recent concept. Current indications of EPO usage are for anemia associated with chronic renal failure, anemia related to zidovudine therapy for patients infected with HIV, and in anemia secondary to cancer chemotherapy.
Patient and Family Education

Patient and family education is critical for the safety and psychological well being of the patient. Table 4 gives a highlight of the main issues to be discussed. Because energy expenditure may need to be minimized, patients should be taught at their own pace, and when they are the most capable of learning and retaining information. As with any group of individuals, assessment of the patient and family readiness to learn and what they need to learn is critical to provide appropriate instruction (VanGulick, 1998).

Conclusion

Fatigue and shortness of breath are the most common presenting symptoms for anemia. A number of basic laboratory tests allow the general practitioner to identify and treat the most common causes of anemia: iron deficiency anemia, and pernicious anemia. Presence of pancytopenia, evidence of bone marrow failure, or possible red cells hemolysis, should prompt an immediate referral to the hematologist for further evaluation, including a bone marrow study. Failure to respond to iron therapy should also be referred to minimize severe risk to the cardiovascular system, especially in elderly.

The advance of biotherapy and more specifically of epoietin alfa represents a major breakthrough in the management of anemia. However, research is needed to evaluate the long-term effect of chronic use of epoietin alfa. Pharmacokinetic studies are also needed to establish dosage guidelines, dose-effectiveness of treatment, and cost analysis.
References


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<td>Hemoglobin</td>
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<tr>
<td>Serum folate</td>
<td>1.9 – 14.0 ng/ml</td>
<td>1.9 – 14.0 ng/ml</td>
</tr>
<tr>
<td>Total iron binding Capacity (TIBC)</td>
<td>250-450 mcg/dl</td>
<td>250-450 mcg/dl</td>
</tr>
<tr>
<td>Transferrin saturation</td>
<td>20% - 50%</td>
<td>20% - 50%</td>
</tr>
<tr>
<td>Iron, serum</td>
<td>65-165 mcg/dl</td>
<td>75-175 mcg/dl</td>
</tr>
</tbody>
</table>

Adapted from Chapman, 1996
Table 2.

Formulas for Reticulocyte counts correction.

Hematocrit correction:

\[
\text{Patient Hematocrit} \times \frac{\% \text{ Reticulocyte}}{45\%} = \text{absolute} \% \text{ reticulocytes}
\]

Reticulocyte "shift" correction:

\[
\frac{\text{Absolute} \% \text{ reticulocytes}}{\text{"Shift" factor}} = \text{Reticulocyte production index}
\]

("shift" factor or maturation time = 1.0 for hematocrit of 45%
1.5 for hematocrit of 35%
2.0 for hematocrit of 25%
2.5 for hematocrit of 15%)

Note: When the Reticulocyte index falls below 2.0, a defect in marrow proliferation or precursor maturation must be present.

Adapted from Hillman, 1998
Table 3. Classification of Common Anemias.

<table>
<thead>
<tr>
<th>Anemia Classification</th>
<th>Differential Diagnosis</th>
<th>Supporting Lab Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microcytic Iron deficiency</td>
<td>Decreased hematocrit &amp; reticulocytes Decreased ferritin, iron, &amp; transferrin. Increased total iron binding capacity (TIBC).</td>
<td></td>
</tr>
<tr>
<td>Thalassemia</td>
<td>Decreased hematocrit &amp; reticulocytes Normal/increased ferritin, normal iron, transferrin, &amp; TIBC.</td>
<td></td>
</tr>
<tr>
<td>Macrocytic Folate deficiency</td>
<td>Decreased hematocrit &amp; decreased to Normal reticulocytes. Increased ferritin &amp; iron, normal TIBC. Decreased folate.</td>
<td></td>
</tr>
<tr>
<td>B12 deficiency</td>
<td>Decreased hematocrit &amp; decreased to Normal reticulocytes. Decreased B12. Increased ferritin &amp; iron, normal TIBC</td>
<td></td>
</tr>
<tr>
<td>Normocytic Anemia of Chronic Disease</td>
<td>Decreased hematocrit &amp; decreased reticulocytes. Increased / normal ferritin Decrease iron &amp; TIBC.</td>
<td></td>
</tr>
<tr>
<td>Hemolytic</td>
<td>Decreased hematocrit, increase reticulocytes Increase lactate dehydrogenase, increased bilirubin.</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Worrall, Tompkins & Rust, (1999)
Table 4.

Patient and family education

Teaching should include:

- Signs and symptoms of anemia
- Importance of maintaining a normal hemoglobin level to minimize risk for syncope, stroke, and heart attack.
- Explain the relationship between anemia, fatigue, and shortness of breath.
- Discuss impact of anemia on quality of life
- Present and explain treatment options, including the purpose, the dose, and the side effects.
- Emphasize the need for testing, describe and explain the blood draws
- Explain the need for bone marrow biopsies, discuss procedure, pain inflicted, conscious sedation, and monitoring. Review the risks and benefits of procedure. Discuss and obtain consent form.
- Emphasize importance of compliance with treatment, treatment schedule, laboratory tests, and follow-up visits.
- Discuss hazards, risks, and benefits of blood transfusions for patients receiving blood products
- Explain relation between nutrients and increased erythrocyte production. Discuss proper nutrition.
- Develop a plan to minimize energy expenditure, including accepting assistance from others, changing lifestyle, instituting safety measures and using assistive devices, grouping activities together, and scheduling intermittent rest periods.

Adapted from VanGulick, 1998
Figure 1. Erythropoiesis Feedback System.

Adapted from Hillman, 1998
Figure 2. Algorithm for anemia.

- **H & P** → NO MASSIVE BLOOD LOSS
- **CBC** with differential → LOW HEMATOCRIT → PANCYTOPENIA → BONE MARROW BIOPSY
- **RETICULOCYTES** → CORRECTED COUNT
  - **LOW**
    - RED CELL MORPHOLOGY
      - NORMOCYTIC → FERRITIN LEVEL → Renal Studies, Erythropoietin, Endocrine studies → Bone marrow
        - Low → Iron deficiency
        - Normal/high → chronic disease, Hemoglobin electrophoresis for Thalassemia → Bone marrow
      - MICRO
      - MACROCYTIC
  - **HIGH** → BLOOD LOSS
  - HEMOLYTIC ANEMIA
    - + COOMBS’ TEST
      - Autoimmune hemolytic anemia 2nd to other disease, drugs, or idiopathic.
      - Exogenous hemolytic factors: burn, strenuous exercise, drug, malaria, septicemia, splenomegaly
      - No exogenous factors: Hereditary hemolytic anemia, Paroxysmal nocturnal hemoglobinuria, Red cell enzymes (G6PD)
Figure 3. The Quality of Life Model

Physical Well-Being
- Energy
- Functional Ability
- Pain
- Sleep and Rest
- Strength

Psychological Well-Being
- Anxiety
- Frustration/Feeling useless
- Coping and Acceptance
- Lost of Independence
- Cognition/Attention
- Depression

Social Well-Being
- Caregiver Burden
- Impact on work/ Financial Impact
- Leisure Activities
- Family Roles & Relationships
- Affection/Sexual Function

Spiritual Well-Being
- Changes in Spirituality
- Altered Priorities to Balance...
- Diminished Energy
- Hopelessness
- Meaning of Fatigue

Adapted from Piper et al., 1987
Appendix

Cancer-Related Anemia
Anemia and Cancer

Anemia is a frequent complication of cancer and its treatment. Nearly 90% of cancer patients will present with anemia during the evolution of their disease (Casadevall, 1998). Cancer-related anemia is typically hypoproliferative and attributable to either direct tumor infiltration of bone marrow, cytotoxic effect of chemotherapeutic agents, or the anemia of chronic disease (ACD).

Tumor infiltration of bone marrow results when healthy marrow is replaced with tumor cells, leading to impaired production of all blood components, including red blood cells. Chemotherapeutic regimens that suppress bone marrow can inhibit the maturation of the erythroid lineage cells. Certain chemotherapeutic agents, such as cisplatin can also decrease red blood cell production by direct nephrotoxic effects that inhibit synthesis and secretion of erythropoietin. However, the most common type of anemia in patients with cancer is ACD (Groopman & Itri, 1999).

ACD is usually characterized by erythroid hypoplasia of bone marrow, decreased reticulocyte levels, and shortened red blood cell survival time. Laboratory findings include declines in hematocrit level, abnormal use of iron, and inadequate erythropoietin serum level for the degree of anemia. Altered iron utilization in cancer patients, leading to hypoferremia combined with either normal or increased amount of stored iron has been reported by Ludwig & Fritz, (1998). Stimulation of the immune system by the malignancy results in the reduced release and availability of iron. The increased levels of inflammatory cytokines, such as interferon-gamma, interleukin-1, and tumor necrosis factor, which occur in cancer, induce leukocytes to produce lactoferrin, which strongly binds the already limited supply of iron.
Cytokines may also inhibit the production of erythropoietin, and is theorized to suppress erythropoiesis at the level of the erythroid precursors, as well as shorten red blood cell survival time (Faquin, Schneider, & Goldberg, 1992). The incidence of chronic anemia in cancer patients depends on the type of malignancy, its stage and duration, the type and intensity of cancer treatment, and on concurrent infections. Prevalence of anemia is low (10% to 20%) in colorectal and breast cancer, but relatively high (50% to 60%) in patients with chronic lymphocytic leukemia, non-Hodgkin’s lymphoma, or multiple myeloma and in patients with ovarian or lung cancer who are receiving chemotherapy (Groopman & Itri, 1999).

**Fatigue: a side effect of anemia**

Fatigue is a universal symptom of illness. Fatigue has been identified as the most prevalent and disturbing symptom of cancer and its treatments (Winningham et al., 1994). Fatigue results in a decreased functional capacity and quality of life for cancer patients. Recent advances in assessing the relationships of anemia, fatigue, and quality of life (QOL) in cancer patients are providing new insights into these closely related factors.

Fatigue is the cardinal symptom of anemia, reported by three of four cancer patients and by those patients afflicted with chronic diseases, such as heart disease, renal disease, lung disease, diabetes, human immuno-deficiency, and others. Ferrell et al. (1996) described the impact of fatigue on the quality of life in cancer patients. Using a convenience sample of 910 men and women, data were obtained from interviews, mail surveys, and focus groups in several QOL studies previously conducted by the investigators and reexamined for fatigue content. A qualitative method of content analysis was used to identify themes associated with the experience of fatigue. The data, organized according to the QOL model previously described by
Piper (1987) and presented in Fig 3, confirmed the hypothesis that fatigue has an impact on physical, psychological, social, and spiritual well-being. Fatigue is reported as a force that affects all dimensions of QOL, rather than being just an isolated physical symptom. Fatigue is generally described as a negative influence on QOL, and interventions to prevent or decrease this symptom is seen as a nursing priority. Furthermore, Ferrell, et al. (1996) suggest viewing fatigue as a human experience rather than an expected and accepted side effect of treatment or as a symptom of disease.

Cella (1997) reported the use of the Functional Assessment of Cancer Therapy (FACT) instrument and its sub-scales for anemia and fatigue (FACT-An & FACT-F) to assess the impact of anemia and fatigue on QOL in 50 patients with a variety of malignancies. Instruments were tested for validity, internal consistency and stability, confirming the reliability of the fatigue component (FACT-F consistency on test-retest: alpha = 0.95 /0.95; FACT-An consistency on test-retest: alpha = 0.96/0.96; validity correlation for both instruments: r = 0.87) (Yellen, Cella, Webster, Blendowsi, & Kaplan, 1997). Patients with hemoglobin levels greater than 12 g/dL reported significantly less fatigue (p = 0.01), better physical (p = 0.003), and functional well-being (p = 0.001), and higher overall QOL measures (p= 0.003) than those with hemoglobin levels less than or equal to 12 g/dL.

EPO, anemia, fatigue, & QOL

With the advent of recombinant human erythropoietin (Epoetin alfa from Amgen Inc. & Procrit from Ortho Biotech Inc.), drug therapy is now available that can decrease and potentially alleviate the need for transfusion in certain patients with anemia. Although erythropoietin treatment has been successfully used for the anemia of renal failure, its application in cancer-
related anemia and fatigue is a more recent concept. Several large, prospective and placebo-controlled studies demonstrating the value of erythropoietin treatment of cancer-related anemia and fatigue are discussed below.

Abels, Larholt, Krantz, & Bryant’s (1991) classic study included 413 patients divided in three treatment regimens: no chemotherapy, non-cisplatin chemotherapy, and myelosuppressive cisplatin-containing chemotherapy. Patients in each group were randomly assigned to receive either placebo or epoetin alfa. In all three groups, patients receiving epoetin alfa had a statistically significant increase in hematocrit compared with placebo-treated patients (p< .004). Furthermore, the rate of RBC transfusions requirement was decreased by 30 to 36 %. QOL parameters measured on a 100mm visual analog scale significantly (p< .05) improved in epoetin-treated patients compared with corresponding QOL changes in placebo-treated patients. A definite strength of the study was the ability to limit uncontrollable variables via the rigorous patient selection criteria including identification of an existing anemic state, absence of occult bleeding, normal kidney function, and absence of organ dysfunction. Nearly 50 % distribution of male versus female subjects, and good representation of various tumor types with 68% of patients having solid tumors, further strengthens this study. However, a disappointing low response rate of 30-36% with erythropoietin treatment, assessed by the need for transfusions, is surprising. This may be explained by the ambitious choice of an arbitrary definition of response, which was an increase in the hematocrit of at least 6 percentage points unrelated to transfusion, or it may be a reflection of the need for a higher dose of erythropoietin to achieve this goal. QOL data and assessment tool were not well defined and the reported improvement was significant only in the overall rating of QOL.
The beneficial effects of epoetin alfa on anemia, functional status, and QOL is further supported by two large, nonrandomized, open-label, multicenter community studies. In one study, Glaspy, Bukowski, Taylor, Tchekmedyian & Vadhan-Raj (1997) evaluated more than 2000 anemic cancer patients with nonmyeloid malignancies, receiving cytotoxic chemotherapy, and treated with epoetin alfa for up to 4 months. The dose was adjusted upward for therapeutic response judged to be inadequate. Patients who received the epoetin alfa treatment had a 1.8 g/dl increase in hemoglobin (p < .001), and fewer transfusions were administered per patient per month after the first month of treatment (p < .001). QOL was measured by using a validated instrument, the Linear Analog Scale Assessment for energy level, activity level and overall QOL. Epoetin alfa treatment was associated with statistically significant increases in energy level (p < .001), activity level (p < .001), and over all QOL (p < .001). Furthermore, a direct and statistically significant correlation was observed between the increase level of hemoglobin and the reported improvement of QOL (energy: r = .3, p < .001; activity: r = .28, p < .001; overall QOL: r = .27, p < .001). In conclusion, this study confirms Abels, et al.’s (1991) observations on the positive effect of epoetin alfa treatment. A definite decrease in the transfusions requirement (35%-50% of patients) was obtained probably related to escalation of the treatment dose of epoetin alfa. A retrospective analysis of 759 patients was conducted to determine the impact of tumor response and physical performance status on the observed improvements in quality of life during epoetin alfa therapy. The results demonstrated that all 759 patients, regardless of tumor response, exhibited a statistically significant increase in energy level. The major limitations of the study included the retrospective collection of data on tumor response and the limited availability of tumor response data. Investigators concluded that more research is needed in this area.
In another study, Demetri, Kris, Wade, Degos, and Cell (1998) prospectively evaluated the potential confounding effect of tumor response in 2289 patients with nonmyeloid malignancies receiving chemotherapy and epoetin alfa for 16 weeks. Statistically significant increases in hemoglobin level (p<.001) and statistically significant decreases in the percentage of patients who required transfusions (p<.001) were observed for all tumor types. QOL was measured by use of two validated instruments, FACT-An and the linear analogue scale assessment (LASA) tool used by Abels et al.,(1990). In addition, Karnofsky's performance status was assessed by the treating physicians. The QOL results were then compared based on the tumor response as being complete, partial, or stable. Epoetin alfa therapy was associated with statistically significant improvements in QOL parameters on both instruments. QOL was statistically significantly correlated (r = .235, p<.001) with an increase in hemoglobin level, regardless of the tumor response (complete, partial or stable). Even patients with progressive disease, whose hemoglobin level increased by at least 2 g/dl were reported to have a better QOL, compared with the patients who had little or no increase in hemoglobin levels. Investigators concluded that both hemoglobin level and disease responses are independent variables that significantly affect QOL. This study reinforces the previously reported benefits of adjunctive treatment with epoetin alfa in cancer patients; it also provides additional evidence of the epoetin alfa benefits on QOL even with progressive disease. Additional pharmacokinetic research is now needed to establish epoetin alfa dosage guidelines and dose-effectiveness of treatment, as well as cost analysis.
Guidelines for treatment of cancer-related anemia

Transfusions

Traditionally, RBC transfusions were the primary treatment available for chronic as well as acute anemia and patients were transfused empirically when hemoglobin concentrations decline below 10 g/dl (Groopman & Itri, 1999). However, concerns about the safety and availability of the blood supply, prompted practitioners to become more conservative with transfusions. The treatment of mild-to-moderate anemia with transfusion was withheld until hemoglobin declined to levels < 8g/dL. This approach is supported by the findings of a multicenter randomized, controlled, clinical trial of transfusion requirements in critical care that involved 838 critically-ill patients with euvolemia. Four hundred eighteen patients were randomly assigned to a restrictive approach for transfusion, in which red cells were transfused if the hemoglobin concentration dropped below 7.0 g/dL and hemoglobin concentration was maintained between 7.0 and 9.0 g/dL. Four hundred twenty patients were assigned to a liberal strategy, in which transfusions were given when hemoglobin concentration fell below 10.0 g/dL, and to maintain hemoglobin concentrations at 10.0 to 12.0 g/dL. The overall 30-day mortality was similar in the two groups (18.7 % vs. 23.3%, p = 0.11). However, the mortality rate during hospitalization was significantly lower in the restrictive-strategy group (22.2 % vs. 28.1%, p = 0.05). The investigators concluded that a restrictive strategy of red-cell transfusion is at least as effective as, and possibly superior to a liberal transfusion strategy in critically-ill patients, with the possible exception of patients with acute myocardial infarction and unstable angina (Hebert et al., 1999). The American College of Physicians’ practice strategies (1992) states that the goal of transfusion is to reach a red blood cell volume that delivers adequate tissue oxygen, maintains an acceptable quality of life, and supports maximum survival from the underlying disease.
Epoetin alfa

Epoetin alfa should be considered for anemic patients whose hemoglobin concentration is less than 10.0 g/dL and are currently receiving blood transfusions and whose lives are affected by the anemia (Koeller, 1998). Baseline hemoglobin/hematocrit (H&H), and baseline endogenous EPO should be determined before starting treatment. An endogenous EPO level of 200 mU/ml or less is predictive of response to therapy. Alternative treatment (e.g. RBC transfusion) should be considered for patients with EPO level >200 mU/ml. Circulating iron and iron-storage capacity should be evaluated and supplemented, if necessary to support erythropoiesis.

The initial dose of EPO should be 150 U/kg given subcutaneously 3 times/week. At the end of 2-4 weeks of therapy, H&H, EPO, ferritin, and reticulocytes should be assessed because early changes may be predictive of response. Reportedly, 79% of patients with a greater than 1.0 g/dL increase in hemoglobin and more than 40,000 reticulocytes/mcL after four weeks of therapy are likely to respond to treatment (Glaspy et al., 1997). Another study of 80 patients with cancer-related chronic anemia reported that, endogenous serum EPO, endogenous ferritin level, and hemoglobin change were the primary determinants in predicting a response to epoetin alfa. After two weeks of therapy, an EPO level of 100 mU/ml or more and an increase in hemoglobin of less than 0.5 g/dL was 90% predictive of treatment failure. A ferritin level of 400 ng/ml or higher, during the same period also predicted lack of response in nearly 90% of patients (Ludwig, et al., 1994). For patients who do respond, epoetin alfa, therapy should be continued with monitoring of H&H and iron every 4 to 8 weeks. The dosage of epoetin should be reduced if hemoglobin increases more than 1.3 g/dL in any 2-week period. If the hemoglobin concentration exceeds 13.0 g/dL, the drug should be discontinued until the hemoglobin falls to 12 g/dL, and then resumed at 75% of the previous dosage. Potential side effects associated with this
agent include an increase in blood pressure, seen in renal patients, but only rarely in the cancer patient population. The risks of polycythemia and elevated plasma viscosity with associated risk for thrombosis, pain, swelling, and irritation at the injection site have been reported only occasionally (Koeller, 1998).

Conclusion

Nurses have been leaders in recognizing the impact of fatigue on the physical, psychological, social, and spiritual well-being of their patients. Leading oncology research nurses have defined the entity of fatigue, analyzed the impact of fatigue in both the healthy and the clinical population. Finally, a number of physical, emotional, and spiritual interventions have been suggested based on fatigue-related research to improve cancer patients’ quality of life.

As mentioned earlier, the advance of biotherapy, and more specifically of epoetin alfa, represents a major breakthrough in the management of anemia. Additional pharmacokinetic research is now needed to establish epoetin alfa dosage guidelines, dose-effectiveness of treatment, and cost analysis. The long-term effect of chronic use of epoetin alfa remains unknown and will have to be evaluated. Additional research is needed in the role of cytokines as chronic anemia causing-agents and their implication in the fatigue phenomena. As cancer-related anemia is being recognized as one of the causative factors for fatigue, it is becoming clear that research outside of the oncology field is needed to evaluate fatigue and its impact on quality of life among other chronically ill patients.

Advanced-practice nurses are instrumental in recognizing the signs and symptoms of fatigue and anemia, and advocating for prompt intervention. Future research on the relationship between hemoglobin levels, patient well-being, and symptoms may leads to new classifications
of chemotherapy-induced anemia. New guidelines would allow more effective therapy not only based on hemoglobin levels, but also based on well-being, therefore enhancing the patient quality of life during and after treatment.
References


