Biology of Anemia, Differential Diagnosis, and Treatment Options in Human Immunodeficiency Virus Infection

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Anemia is the most common hematologic manifestation of human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome. The causes of HIV-related anemia are multifactorial and include direct and indirect effects of HIV infection. HIV-related anemia generally is due to reduced red blood cell (RBC) production, secondary to a variety of causes, but it may also involve nutritional deficiencies, increased RBC destruction, or a combination of these problems. Evaluation of hemoglobin level, reticulocyte count, bilirubin, and mean corpuscular volume value and review of the peripheral blood smear are necessary for diagnosis. Treatment of HIV-related anemia should address the correctable underlying causes of this disorder, such as modifications of offending medications, nutritional deficiencies, and parvovirus infection. Patients with HIV infection have a blunted erythropoietin response to anemia. Therapeutic modalities for anemia that is not amenable to correction include blood transfusion and recombinant human erythropoietin (epoetin alfa).

Introduction

Hematologic abnormalities, including anemia, are common manifestations of human immunodeficiency virus (HIV) infection and AIDS [1]. Anemia can impact daily quality of life by inducing such symptoms as loss of stamina, rapid heart rate, and shortness of breath [2, 3]. Anemia has been shown to be a risk factor for early death in patients with AIDS [4]. The diagnosis and treatment of anemia are essential in the medical care of the HIV-infected patient; thus, it is critical that clinicians who treat HIV-infected patients understand the biology of anemia, the differential diagnosis of this condition, and the treatment options for patients with HIV-related anemia.

The Biology of HIV-Related Anemia

The causes of HIV-related anemia are multifactorial [1, 5–8]. HIV may directly affect bone marrow stromal cell or cause cytokine secretion, leading to decreased production of red blood cells (RBCs) and other bone marrow elements. Tumor necrosis factor and other cytokines inhibit hematopoiesis, and cytokine levels are elevated in HIV disease. Treatment of HIV and reduction of virus load by the use of highly active antiretroviral therapy may improve hematopoiesis [9]. Patients with HIV may also acquire chronic parvovirus B19 infection, resulting in profoundly decreased numbers of RBCs. In addition, anemia may result from the indirect effects of HIV infection, such as adverse reactions to medications, opportunistic infections, neoplasms, or nutritional abnormalities stemming from anorexia, malabsorption, or metabolic disorders. Although many drugs used to treat HIV-related disorders are myelosuppressive, severe anemia is most often related to the use of zidovudine [4, 10].

Alterations in the components of normal erythropoiesis, which include an adequate supply of iron, folate, and vitamin B12, an intact bone marrow, and the essential hematopoietic growth factor, erythropoietin, may produce anemia [2]. The production of RBCs requires normal bone marrow function; thus, the bone marrow must be free of infection and tumor. Renal production of erythropoietin is required to stimulate the erythroid bone marrow precursors to proliferate and increase RBC production. Thus, severe renal insufficiency will also contribute to anemia in HIV-infected patients. Under normal circumstances, the production of erythropoietin changes in accordance with oxygen delivery. For example, if the hemoglobin level decreases below 12 g/dL, erythropoietin concentrations increase [11].

Although HIV-related anemia ultimately is often attributed to reduced RBC production, it is important to remember that other conditions, such as hemolysis or gastrointestinal bleeding, may also occur in these patients [10]. For example, thrombotic thrombocytopenic purpura, an antibody-mediated microangiopathic hemolytic anemia, is seen with increased frequency in HIV-positive patients [1]. One-third of HIV-infected patients may have a positive Coombs test, indicating RBCs coated with immunoglobulin. However, these patients rarely have clinically apparent autoimmune hemolytic anemia [1].

Many patients with HIV-related anemia have what is referred to as “anemia of chronic disease” because there is often a reduction in RBC production and a suppression of reticulocyte response secondary to chronic HIV infection [1, 12, 13]. This is accompanied by a blunted erythropoietin response per level of hemoglobin, which is not related to chronic inflammation or infection such as would be seen in iron-deficiency anemia [14].
**Differential Diagnosis of Anemia in HIV-Infected Patients**

The differential diagnosis of anemia in HIV is often multifactorial and may ultimately require multiple evaluations by the clinician. Often patients are being treated with multiple medications and may have more than one co-morbid condition. Algorithms for the evaluation of anemia in patients with HIV infection are shown in figures 1 and 2 [10]. Anemia is defined as a hemoglobin level of <14 g/dL in men and <12 g/dL in women [15]. The reticulocyte count will distinguish patients with active bone marrow that is responding to the anemia (e.g., counts above 2%) from those with suppressed bone marrow (e.g., counts below 2%). For many patients with HIV infection, the reticulocyte count will be low, suggesting suppressed bone marrow. Such patients can be further distinguished on the basis of mean corpuscular volume (MCV) values. Patients with low MCV values may have iron deficiency secondary to chronic blood loss or thalassemia. Thalassemia is more likely to occur in patients of African, Mediterranean, or Southeast Asian ancestry [16]. Patients with normal MCV values may have anemia of chronic disease—suppressed bone marrow due to the chronic release of cytokines during infection or inflammation, use of drugs that induce anemia, or abnormalities in the bone marrow, such as infection or tumor infiltration. These latter patients will generally be neutropenic and/or thrombocytopenic as well. Last, patients with high MCV values and low reticulocyte counts may have drug-induced anemia (most commonly due to zidovudine or similar medications) or anemia due to vitamin B12 or folic acid deficiency. Liver disease and alcohol abuse will also present with macrocytosis. Myelodysplasia may present occasionally with an elevated MCV, although this marrow abnormality is not known to be a direct consequence of HIV infection.

For the few patients who present with low hemoglobin levels and high reticulocyte counts, consideration should be given to conditions that result in RBC destruction or loss. Such conditions may include autoimmune Coombs-positive hemolysis and microangiopathic hemolytic anemia that develops subsequent to disseminated intravascular coagulation or to thrombotic thrombocytopenic purpura. RBC destruction or loss can also occur in glucose-6-phosphate dehydrogenase–deficient male patients who are administered oxidant drugs (i.e., trimethoprim-sulfamethoxazole, diaphenylsulfone). Blood loss may be due to gastrointestinal losses in patients with a variety of causes, including cirrhosis, Kaposi’s sarcoma, or lymphoma. Last, reticulocytosis would be expected to occur in patients with nutritional deficiencies who are responding to therapy.

When evaluating a patient with anemia, it is important to distinguish the anemia of chronic disease from that caused by iron deficiency because the clinical implications and treatment of...
these conditions are quite different. Although both disorders induce a low serum iron level, other laboratory findings differ [12, 17]. Patients with low total iron-binding capacity and serum ferritin levels < 100 μg/L are unlikely to have iron deficiency. If the diagnosis is unclear on the basis of laboratory findings, it is acceptable to supplement the patient with iron for 7–10 days and re-evaluate the anemia on the basis of changes in iron status. Bone marrow examination may be required to evaluate iron stores.

Parvovirus B19, a ubiquitous virus with a tropism for erythroid precursors, can cause profound anemia in HIV-positive patients [1]. Unable to clear the virus, these patients may present with hemoglobin levels < 5 g/dL. Diagnosis is best made on the basis of bone marrow biopsy, which reveals giant pronormoblasts. Treatment includes prompt transfusion and intravenous gamma globulin. The latter contains high titers of antiparvovirus antibodies.

**Figure 2.** Evaluation of anemia in patients with HIV infection and high reticulocyte counts. Hb, hemoglobin; RBCs, red blood cells.

**Treatment Options for Patients with HIV-Related Anemia**

As with any medical intervention, treatment of HIV-related anemia should be chosen to address the underlying cause of this disorder [1, 4]. For example, patients with iron or vitamin B₁₂ deficiency will respond to appropriate replacement therapy. Patients may benefit from nutrient supplements, or patients with anemia that appears to be related to myelosuppressive drug therapy may benefit from a switch to drugs with fewer myelosuppressive properties. However, switching antiretroviral agents may have serious implications for therapeutic efficacy and future treatment. Therefore, a more appropriate approach may be to utilize therapy designed to improve anemia. Such therapeutic modalities include blood transfusion, recombinant human erythropoietin (epoetin alfa), and androgens.

**Blood transfusion.** The conventional treatment for severe anemia is blood transfusion [5]. Although there are remote risks associated with blood transfusions, such as the transmission of blood-borne viruses [18, 19] and the rare transfusion reaction [20], transfusions are usually well tolerated [1, 16]. There have been reports that blood transfusion is immunosuppressive [18, 21, 22], but this is controversial [23]. Transfusion is used for patients who are symptomatic from anemia and who may be experiencing cardiac or respiratory compromise. The decision to transfuse is physician-dependent, but most clinicians would transfuse patients with a hemoglobin level of < 8 g/dL.

**Epoetin alfa.** Epoetin alfa does not induce the adverse effects associated with transfusion [1, 24, 25]. However, it generally takes 4–8 weeks for the effects of epoetin alfa to be clinically meaningful. This may be unacceptable for the symptomatic patient with anemia. The results of clinical trials with epoetin alfa demonstrate its efficacy and safety for patients with mild symptomatic or moderate HIV-related anemia, as well as its ability to reduce or eliminate the requirement for further transfusion in some severely anemic patients. A recent study demonstrated improvement in quality of life measurements for those patients using epoetin [26]. Erythrocytosis and secondary polycythemia can result if the patient is not carefully monitored and if doses are not adjusted as needed [24].

Henry et al. [27] conducted a combined analysis of 255 HIV-infected patients who received zidovudine therapy in 4 separate but similar trials of epoetin alfa. In this study, patients with low
endogenous erythropoietin levels at baseline (e.g., values ≤ 500 IU/L) who were treated with epoetin alfa (100–200 U 3 times a week) had significant increases in mean hematocrit values compared with those receiving placebo (P = .0002) (figure 3). The average difference in hematocrit value at week 121 was 3.9% (95% confidence interval, 1.8–6.0). Hematocrit values were greater in the epoetin alfa–treated patients than in the placebo-treated patients as early as 3 weeks after initiation of treatment. At the end of the 12-week study period, mean hematocrit values were .32% for epoetin alfa–treated patients, compared with a mean baseline value of 27.5%. Furthermore, significantly fewer transfusions were required for epoetin alfa– compared with placebo-treated patients (3.2 vs. 5.3 U, P = .003). Overall, no important differences in the incidence or severity of adverse events were observed in epoetin alfa– compared with placebo-treated patients. The results of this analysis suggest that therapy with epoetin alfa is safe and can increase mean hematocrit values and reduce transfusion requirements in zidovudine-treated patients with HIV-related anemia.

In another study, an analysis of 523 patients who were not taking zidovudine at baseline or during the study demonstrated that both the efficacy and safety of epoetin alfa in these patients were similar to those observed in zidovudine-treated patients [28]. Interim data from a recent study suggest that once-weekly dosing of epoetin alfa (40,000 U) can improve anemia in HIV-infected patients to the extent observed with thrice-weekly dosing [29, 30]. This finding is similar to those in studies of anemic cancer patients undergoing chemotherapy [31]. Last, it should be noted that patients treated with epoetin alfa require iron supplementation to meet the demand for iron during enhanced RBC production [23, 24]. Iron should be given for the first 2 months of therapy, and may be required again after this time.

**Androgens.** Oxymetholone and other anabolic steroids have been used to treat anemia [32]. These agents can increase production and urinary excretion of erythropoietin in patients with anemia caused by bone marrow failure, and they can stimulate erythropoiesis in patients with deficient RBC production. Androgens are contraindicated in patients with breast or prostate cancer, pregnant women, and pediatric patients because of their effect on bone maturation. Long-term use of androgens has been associated with hepatotoxicity, hepatocellular cancer, peliosis hepatitis, jaundice, atherosclerosis from blood lipid alterations, and virilization in women [32]. Patients who use this or other forms of androgens for wasting or testicular failure must be followed carefully, especially if given erythropoietin. Polycythemia may result from their use and require phlebotomy.

**Conclusions**

Anemia is a common and debilitating condition associated with HIV infection. Differential diagnosis of HIV-related anemia permits selection of appropriate treatment regimens by determining the etiology of the disorder. Treatment regimens for HIV-related anemia should address the underlying cause and may include dietary iron supplementation, modulation of medications, and specific treatment of underlying causes, such as parvovirus or opportunistic infections. Therapeutic modalities used to treat HIV-related anemia include blood transfusion, epoetin alfa, and androgens. Blood transfusion is the standard of care for severely anemic patients. Androgens can stimulate erythropoiesis in patients with deficient RBC production, but use of these has been associated with serious adverse events and is not recommended as primary therapy for HIV anemia. Epoetin alfa can ameliorate HIV-related anemia and is well tolerated. In summary, differential diagnosis and proper treatment...
of HIV-related anemia are critical components of healthcare management for HIV-infected patients.

References