REVIEW ARTICLE

Anaemia in Human Immunodeficiency Virus Infection: A Review

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ABSTRACT

Background: *Human immunodeficiency virus infection is associated with myriads of haematological abnormalities and complications, including anaemia. This review aims at presenting the epidemiologic evidence of HIV associated anaemia, and also examine its effects on patients' survival and the need for specific diagnosis and treatment.*

Methods: *A review of relevant literature on the subject was sourced manually and by PUBMED internet search. The following keywords were used for internet search: anaemia, chronic disease, highly active antiretroviral therapy, human immunodeficiency virus, haematological abnormalities, and AIDS.*

Results: *Human immunodeficiency virus (HIV) is associated with numerous abnormalities of red blood cells production and lifespan. One of these consequences is anaemia. The prevalence of these estimates varies widely from one population to another; however, anaemia was consistently shown to be a predictor for increased disease progression and decreased survival of patient infected by HIV.*

Conclusion: *Regular evaluation of patients infected by HIV is necessary, to determine the specific causes of anaemia in order to ensure the institution of appropriate intervention.*

KEYWORDS: Anaemia; HIV and HAART

Paper accepted for publication 18th July 2006.

INTRODUCTION

Human immunodeficiency virus (HIV) is associated with numerous abnormalities of haematopoiesis, affecting both the myeloid and lymphoid lineages derived from the haematopoietic stem cell. Thus as many as 70% to 80% of HIV-infected patients develop anaemia during the course of infection. The aetiologies of these abnormalities are diverse[1,2]. First, while initially controversial, [3-5] there is recent evidence to indicate that the haematopoietic stem cell or CD34+ progenitor cell is resistant to infection by HIV[6]. However, more committed myeloid progenitor cells may be infectable, and are clearly functionally abnormal, with marked colony growth[3,7]. Likewise, the microenvironment of the marrow, necessary for normal blood cell growth and development, is also abnormal. All these factors, along with numerous additional abnormalities, eventually lead to the frequent development of cytopenias, including anaemia. In this review, we would present prevailing opinions on the epidemiology of anaemia in HIV infection, and also examine its implication to patient survival and the need for treatment.

Incidence of Anaemia in HIV Infection

The prevalence of anaemia varies depending on whether the data reported are from before or after the highly active antiretroviral therapy (HAART) era[8]. In an Antiretroviral pilot study conducted in Nigeria, Erhabor and coworkers[9], found a prevalence of 80% of anaemia among antiretroviral naïve patient at base line. In a large observational cohort, medical records were evaluated for 32,867 patients with HIV who received medical care from January 1990 - August 1996 in clinics, hospitals, and private medical practices in nine cities in the United States[10]. Haemoglobin levels were below normal (men < 14 g/dl, women < 12 g/dl) in 55% of patients with immunologic acquired immunodeficiency syndrome (AIDS) and 87% of patients with clinical AIDS. Anaemia was defined as a haemoglobin level of less than 10 g/dl or a diagnosis of anaemia based on International Classification of Disease, Ninth Revision codes. In this study, the 1-year prevalence of anaemia, calculated in the pre- HAART era, was 36.9% for patients with clinical AIDS (one or more AIDS-defining opportunistic illnesses as classified by the Centers for Disease Control and Prevention [11], 12.1% for patients with immunologic AIDS (CD4+ cell count of < 200 cells/mm^3 or CD4+ T Lymphocyte less than 14% but not clinical AIDS), and 3.2% for persons with HIV infection but not AIDS. In addition, 22% of patients had drug-related anaemia, which was associated with zidovudine, fluconazole, and / or ganciclovir.

Most of the literature regarding HIV-related anaemia originated in the pre-HAART era. Since HAART has become the standard of care for patients with HIV, several studies have examined its impact on anaemia [12,-14]. In one study, HAART was begun in 1624 patients with HIV[14]. Before treatment, 64.0% of patients had mild anaemia and 1.5% had severe anaemia. Six months after the introduction of HAART, these proportions decreased to 52.0% and 1.2% and at 12 months were 45.6% and 0.6% respectively, suggesting that HAART may improve haemoglobin levels and correct anaemia in some patients with HIV. Among individuals who inject drugs and have HIV, one group of authors demonstrated a change in haemoglobin concentrations after HAART began[12], from baseline to the last follow-up visit, the haemoglobin concentration had increased by 3.6 ± 1.7 g/dl in 102 patients receiving HAART and decreased by 4.2±1.1 g/dl (p = 0.04) in 103 patients not receiving antiretroviral therapy during a mean follow-up of 1 year (range 0.87-1.21 years). However, at the last study visit, 38.2% of subjects in the HAART group were still anaemic

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(haemoglobin level for men < 13 g/ dl and for women < 12 g/dl).

Another group evaluated the effects of HAART on haemoglobin levels in 905 patients with HIV[13]. At baseline, 11% , 28% , 39% , and 21% of patients receiving HAART and 9% , 24%, 44%, and 23% of patients not receiving HAART had haemoglobin levels of 10 g/dl or less, 10.1-12 g/ dl, 12.1-14 g/dl, and greater than 14 g/dl , respectively. After 1 year, 42% of patients who received HAART and 31% of patients who did not receive HAART had haemoglobin levels greater than 14 g/dl (p = 0.0006). The median increase in haemoglobin level was 1.1 g/dl in patients who received HAART compared with 0.5 g/dl in patients who did not receive HAART (p= 0.001), and this improvement occurred irrespective of zidovudine in the regime. In summary, the available evidence suggests that HAART is associated with improvement in haemoglobin levels in most patients with HIV. The prevalence of severe anaemia has decreased in the HAART era; however, mild- to- moderate anaemia remains common.

Causes and Mechanisms of Anaemia in HIV-Infected Patients

Numerous causes of anaemia exist in HIV-infected patients, which follows one of, or a combination of mechanisms. These include

- Decreased RBC production;
- Ineffective RBC production
- Increased RBC destruction

Anaemia due to decreased production of RBCs

A decrease in production of RBCs may result from factors suppressing the haematopoietic or myeloid progenitor (CFU-GEMM), such as inflammatory cytokines or HIV itself[1,2]. In addition, a blunted production of erythropoietin has been documented in anaemic HIV-infected patients[15]. Infiltration of the marrow by tumor, such as lymphoma, [16] and by infection such as *Mycobacterium avium* complex (MAC), may also lead to the decreased production of RBCs, tumor may also lead to chronic blood loss, with eventual iron deficiency anaemia. Another prominent cause of hypoproliferative anaemia in patients with HIV infection is the common use of multiple medications, many of which may cause marrow and /or RBC suppression. Zidovudine (AZT), one such medication, is uniformly associated with macrocytosis (mean corpuscular volume [MCV] >100 fl), a condition which can be used as an objective indication that the patient has been compliant with this medication[17]. Infection of the marrow by parvovirus B19 is another cause of hypoproliferative anaemia in HIV- infected patients, resulting in specific infection of the earlier recognisable RBC precursor, the pronormoblast[3].

Anaemia due to increased RBCs destruction (Haemolytic Anaemia)

Increased RBC destruction may be seen in HIV-infected patients with glucose-6- dehydrogenase (G6PD) deficiency who are exposed to oxidant drugs and in HIV- infected patients with disseminated intravascular coagulation (DIC) or with thrombotic thrombocytopenic purpura (TTP)[18]. Presence of fragmented RBCs and thrombocytopenia on blood smear will be seen in the latter 2 conditions, and Heinz bodies are seen in association with G6PD deficiency. Hemophagocytic syndrome has also been described in association with HIV infection, with actual phagocytosis of RBCs by macrophages within the marrow. An additional cause of RBC destruction leading to anaemia in HIV infected patients is the development of autoantibodies, with resultant positive Coombs' test and shortened RBC survival. Of interest, presence of antibody coating the RBC surface (positive direct Coombs' test) has been reported in as many as 18% of 77% of HIV- infected patients, although the incidence of actual haemolysis, or RBC destruction, is extremely low. When present, anti-i antibody and antibody against auto-U antigens have been described, occurring in 64% and 32% of HIV infected patients, respectively[19]. A high incidence of positive direct Coombs' test has also been detected in patients with other hypergammaglobulinemic states, however, indicating that the positive Coombs' in HIV may simply be secondary to the polyclonal hypergammaglobulinemia known to occur in the setting of HIV infection[3].

Anaemia due to ineffective production of RBCs (B12 and or Folic Acid deficiency)

Folic acid is absorbed in the jejunum and is responsible for one carbon transfer required in the synthesis of DNA. A deficiency of folic acid leads to a megaloblastic anaemia, with large oval RBCs in the blood, hypersegmented polys, and a decrease in all 3 lines, with resultant anaemia, neutropenia, and thrombocytopenia [3]. Folic acid is found primarily in green, leafy vegetables, and is heat labile. Since tissue stores of folate are relatively small, a deficiency of folate from the diet, lasting as little as 6-7 months, may lead to anaemia. It is thus apparent that HIV infected patients who are ill and unable to eat optimally, as well as those with underlying disease of the jejunum may be unable to absorb sufficient folic acid; this lack of absorption may lead to anaemia. In folic acid deficiency, the reticulocyte count is low, while the indirect bilirubin level will be elevated. The MCV of the RBCS will be high. The classic changes of megaloblastic anaemia will be detected on examination of the bone marrow, while serum and RBC folate levels will be low[3].

Ineffective production of RBCs, with pancytopenia in the blood, elevated indirect bilirubin level, and low reticulocyte count may also be seen in vitamin B12 deficiency. The absorption of B12 requires initial production of intrinsic factor by parietal cells in the stomach, with subsequent absorption of the complex of B12 and intrinsic factor within the ileum. Thus, malabsorption of B12 can occur relatively easily in various disorders of the stomach (achlorhydria); by production of antibodies to intrinsic factor or to parietal cells ("pernicious anaemia"); or by various disorders of the small

bowel and ileum (Crohn's disease). While B12 deficiency is highly unlikely on a dietary basis alone, patients with HIV infection appear to be prone to B12 malabsorption, presumably due to the myriad of infections and other disorders that may occur in the small intestine of such individuals. Negative vitamin B12 balance has been documented in approximately one third of patients with AIDS, the majority demonstrating defective absorption of the vitamin[3]. Diagnosis of B12 deficiency can be made by documenting low serum B12 levels, while the earliest indication of negative B12 balance is the finding of low B12 level in blood in patients taking transcobalamin II. Monthly administration of parenteral B12 will correct the deficiency as well as the resultant anaemia and pancytopenia in the peripheral blood. Since B12 deficiency may also cause neurologic dysfunction (subacute combined degeneration of the cord), with motor, sensory, and higher cortical dysfunction, the possibility of vitamin B12 deficiency should also be considered in HIV infected patients with these neurologic symptoms[3].

Impact of Anaemia on Patient Survival

Three large observational cohort studies found that anaemia was an independent predictor of decreased survival and disease progression in patients with HIV[10,14]. In a cohort of 19,213 patients, the median survival was significantly shorter in patients with anaemia than in those without anaemia[10]. This was independent of CD4+ count, Clinical AIDS, age, neutropenia, thrombocytopenia, antiretroviral therapy, and *P. carinii* pneumonia prophylaxis. Compared with patients without anaemia, the risks of death was 148% (99% confidence interval [CI] 114-188) and 56% (99% CI 43-71) greater in anaemic patients with CD4+ counts of greater than or equal to 200 cells/mm^3 or less than 200 cells/mm^3, respectively.

A similar observational prospective trial, conducted in Europe described changes in haemoglobin levels over time in 6275 patients with HIV[14]. Normal haemoglobin level was defined as greater than 14g/dl for men and 12g/dl for women; mild anaemia was 8-14 g/dl for men and 8-12 g/dl for women; severe anaemia was defined as less than 8 g/dl for both men and women. At 12 months, more patients with mild or severe anaemia had died compared with patients without anaemia (15.9% 95% CI 14.5-17.2 and 40.8%, 95 CI 27.9-53.6 vs. 3.1%, 95% CI 2.3-3.9, and $p < 0.001$). In a multivariate time updated Cox proportional hazards model adjusted for CD 4+ cell count and viral load, a 1-g/dl reduction in haemoglobin level increased the hazard of death by 57% (relative hazard 1.57, 95%, 95% CI 1.4-1.75, $p < 0.0001$). Therefore, it was concluded that haemoglobin concentration was a strong independent prognostic marker of death[13].

In a study designed to develop a prognostic scoring system to assess the risk of clinical progression (new AIDS defining illness or death) over time for patients receiving HAART[20], 2027 patients who started HAART during a prospective follow-up were evaluated. Results were confirmed in two other cohorts of patients. Four factors were identified as independently related to the risk of disease progression: the most recent CD4+ count, viral load, haemoglobin level, and a diagnosis of severe AIDS before the start of HAART; furthermore, mild anaemia was associated with a relative hazard of disease progression or death of 2.2 (95% CI 1.6 2.9, $p < 0.0001$) in contrast to a relative hazard of 7.1 for severe anaemia (95% CI 2. 5-20.1, $p = 0.0002$).

Limitations to these studies include variation in definitions of anaemia and possible causes of anaemia, as well as an observational cohort study design, which cannot conclusively answer if the relationship between anaemia and decreased survival is causal[21]. Despite the study designs all of the studies consistently found anaemia to be associated with decreased survival, independent of other prognostic factors.

Importance of Treatment

Fatigue, one of the cardinal symptoms of anaemia, is a common symptom of HIV infection and is associated with impaired physical functioning and reduced quality of life[22]. One group of authors examined the prevalence of fatigue and its medical and psychologic correlates in 427 ambulatory patients with AIDS[22]. Based on responses to fatigue items on two separate assessment tools, 52.7% of patients were classified as having fatigue. Furthermore, fatigue was significantly associated with lower levels of serum haemoglobin, suggesting anaemia as a possible cause of fatigue in some patients ($p < 0.02$). Owing to the high prevalence of anaemia and fatigue among patients with HIV infection, treatment of anaemia may alleviate fatigue in certain patients and improve quality of life.

The finding from the epidemiologic studies presented earlier provides consistent evidence that an association between anaemia and decreased survival and disease progression exists in patients with HIV. Recovery from anaemia also has been linked to improved survival outcomes[10, 21]. In an observational cohort, follow-up haemoglobin levels were available for 3203 patients with anaemia[10]. Of these patients, 1341 were treated with either recombinant-Human Erythropoietin (r-HuEPO) or blood transfusion, and 1208 recovered (haemoglobin level > /= 10 g/dl) and reached a haemoglobin level that was 1 g/dl or more, higher than baseline. After controlling for clinical AIDS diagnosis, CD4+ cell count, neutropenia, thrombocytopenia, antiretroviral therapy, and *P. carinii* pneumonia prophylaxis, recovery from anaemia was significantly associated with a reduced risk of death ($p=0.0001$). In another study[23], the authors used data from an observational study (2348 patients) and also analyzed haemoglobin levels for 91 anaemic patients treated with r-HuEPO for an average of 6months (range 2 wks 28 mo.) Mean haemoglobin level in patients treated with r-HuEPO increased by 1.5 g/dl (range 0.207.1 g/dl, and treatment with r-HuEPO was associated with a significantly reduced risk of death (relative hazard

0.57, range 0.40-0.81, p= 0.002) compared with no r-HuEPO treatment. This survival benefit was maintained even after controlling for other confounding variables. Even though epidemiologic studies alone cannot establish causality, it appears that the treatment of anaemia is an important clinical consideration for health care providers[3,13].

CONCLUSION

HIV infection is associated with myriads of abnormalities related to haematopoiesis. These include aberrations of various haematopoietic progenitor cells, disturbance of the microenvironment of the bone marrow, and abnormal production of various haematopoietic growth factors that influence blood cell production and function. In addition, the presence of various infections or malignancies may alter blood cell production; while the numerous medications employed in HIV infected patients may also affect normal haematopoiesis. Specific evaluation of patients affected to determine the specific cause of anaemia is therefore necessary in order to ensure appropriate intervention.

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