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Anaemia in Persons with HIV Infection: Prognostic Marker and Contributor to Morbidity

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Abstract

Human immunodeficiency virus (HIV)-infected patients experience a range of haematological complications including anaemia, neutropenia, lymphopenia and thrombocytopenia. Anaemia is a prognostic marker of future disease progression or death, independent of CD4 and viral load. Recovery from anaemia reduces the risk of disease progression to approximately the same level as seen among patients who have never had anaemia. Additionally, anaemia impacts a range of dimensions of quality of life, most commonly through fatigue. Anaemia can be caused by a range of mechanisms including infections, neoplasms, dietary deficiencies, blood loss and medication. Histologically, bone marrow hypoproliferation and dysplasia are the most commonly seen. Both AZT and d4T induce macrocytosis, however, AZT, but not d4T, has broader myelosuppressive effects both in vitro and in vivo. The management of anaemia typically includes correction of the underlying cause(s) and blood transfusion or erythropoietin. However, blood transfusions and iron supplementation may activate HIV expression and possibly worsen immunosuppression. Recombinant human erythropoietin (rHuEPO) is an effective means of improving haemoglobin and reducing transfusion requirements in patients who have low (<500 IU/L) endogenous erythropoietin levels.

Key words

HIV. Anaemia. Zidovudine. Erythropoietin. Prognosis.

Introduction

The hematologic complications of human immunodeficiency virus (HIV)-infected patients include anaemia, neutropenia, lymphopenia and thrombocytopenia. Early in the HIV pandemic it was recognised that anaemia was a prognostic marker of future disease progression or death, independent of CD4 and viral load. This observation remains true in the HAART era. Additionally, anaemia impacts a range of dimensions of quality of life[1] most commonly due to its association with fatigue. Recovery from anaemia reduces the risk of disease progression to approximately the same level as seen among patients who have never had anaemia[2].

Definitions for anaemia normally use the level of haemoglobin (Hb) as the standard. This is normally in the range of 16 ± 2 g/dL for men and 14 ± 2 g/dL for women. WHO/ACTG toxicity grades for anaemia are shown in table 1. The percentage of erythrocytes in relation to the total blood volume (haematocrit) normally ranges from 47% ± 5% for men and

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42% ± 5% for women. The mean corpuscular volume (MCV) is used as a pointer to distinguishing between the different types of anaemia, the normal range being 80-95 fL. Lower MCV (microcytic anaemia) is associated with iron deficiency and elevated MCV (macrocytosis) typically with vitamin B12 or folate deficiency although in the setting of HIV treatment often simply reflects use of AZT or d4T. The grading of anaemia relative to normal ranges may leave some individuals in a grey area where their haemoglobin values fall below the laboratory normal range but not necessarily into the grade 1 toxicity range. However, studies in both HIV and other areas of medicine indicated that values for haemoglobin immediately below the normal range are often associated with symptoms, especially fatigue or with diminished quality of life.

Anaemia can be caused by a range of mechanisms including infections, neoplasms, dietary deficiencies, blood loss and medication[3]. Histologically, bone marrow hypoproliferation and dysplasia are most commonly seen. Inhibition of erethrocyte progenitor cell differentiation in the bone marrow by HIV or *Mycobacterium avium* complex (MAC) infection may reduce red blood cell production. AZT and d4T both induce macrocytosis, however, AZT, but not d4T, has broader myelosuppressive effects both *in vitro* and *in vivo.* Chronic disease is commonly associated with anaemia often in conjunction with low erythropoietin levels. Additionally, other cytokines such as tumour necrosis factor a and transforming growth factor b may be upregulated in HIV infection, contributing to ineffective red cell production. Deficiencies in iron, vitamin B12 or folate are infrequent in HIV infected persons in the developed world. Iron deficiency most commonly being related to blood loss and vitamin deficiencies to malabsorption secondary to severe gastrointestinal infections such as with crypto- or micro-sporidia.

In the era of highly active antiretroviral therapy (HAART) anaemia continues to contribute to morbidity and diminished quality of life. The relative contributions of infection and drugs to risk of anaemia, however, is likely to have changed relative to the mono- and dual therapy eras.

The management of anaemia typically includes correction of the underlying cause(s) and blood transfusion or erythropoietin. However, it appears that blood transfusions may directly accelerate HIV disease progression through activation of HIV expression and possibly by triggering immunosuppression[4]. Supplementation with iron should also be done with caution, as iron could be harmful to persons with HIV infection, being associated in some studies with increased progression risk[5]. Recombinant human erythropoietin (rHuEPO) is an effective means of improving haemoglobin and reducing transfusion requirements in HIV-infected patients who have low (≤500 IU/L) endogenous erythropoietin levels[6] although this approach comes with a significant cost burden (albeit offset against immediate and subsequent transfusion costs).

This review will examine the evidence for anaemia as an independent predictor of poor clinical outcome in persons with HIV, discuss the mechanisms and risk factors for anaemia and the management options for avoiding and treating anaemia.

Main Mechanisms

Erythrocyte numbers are continuously adjusted to optimise oxygen carriage capacity by hormonal messages in the form of erythropoietin transmitted to the bone marrow from an oxygen sensor in the kidney. In the bone marrow, erythropoietin binds to and activates specific receptors on the erythroid progenitor cells. These progenitor cells then develop into mature erythrocytes and are released into circulation as reticulocytes[7]. The circulating life of an erythrocyte is generally considered to be around 120 days.

It is not in the scope of this review discuss the general causes of anaemia, only those common in or pertinent to HIV infection. The main causes on anaemia in the setting of HIV include anaemia of chronic disease (usually erythropoietin deficient anaemia), bone marrow infections (parvovirus B19, cytomegalovirus, *Mycobacterium avium, Cryptococcus neoformans),* neoplasms especially lymphoma, malnutrition and malabsorption, myelosuppressive drugs, histiocytosis, myelofibrosis and myelodysplasia[3]. Cytokines such as interleukin-1, tumor necrosis factor and the interferons play and important role in impairing erythropoietin response by rducing concentrations of marrow progenitors and erythroid colonies, and effecting abnormalities of reticuloendothelial iron metabolism[8]. As HAART generally diminishes these cytokines it is not surprising that erythropoietin deficient or resistant anaemia is less common in recent surveys than in the pre-HAART era and that anaemia may improve under the influence of HAART. Additionally, with the decline in opportunistic diseases, neoplasms and infection-related nutrient malabsorption secondary to HAART, the relative contribution of these problems to the incidence of anaemia is declining. This leaves drugs as the key contributors.

Table 1. *WHO/ACTG Anaemia Grades.*

Grade	Haemoglobin range
Grade 1	9.5-10.5g/dl (upper limit may depend on laboratory range)
Grade 2	8.0-9.4g/dl
Grade 3	6.5-7.9g/dl
Grade 4	<6.5g/dl

A range of medications used in the HIV setting may contribute to anaemia. Commonly used myelosuppressive drugs are listed in table 2. The effects of co-prescription of myelosuppressive agents is likely to be at least additive on the rates of anaemia development.

AZT remains the most widely used myelosuppressive drug in HIV patients. There appears several possible mechanisms by which this agent may cause anaemia. The anaemia associated with AZT therapy is due to red cell hypoplasia or aplasia. Bone marrow examination may demonstrate pure red cell aplasia, erythroid maturation arrest, erythroid hypoplasia and megaloblastic erythropoiesis. Erythropoietin levels are normal or increased[9]. Thus, evaluation of erythropoietin may help guide investigation into the cause of anaemia. One study of anaemia in 110 persons with HIV indicated that symptomatic patients not receiving AZT therapy demonstrated a strong inverse relationship between serum erythropoietin and hemoglobin levels whereas those who were anaemic whilst receiving AZT demonstrated serum erythropoirtin levels that ranged from normal to markedly elevated (9-3,390 mU/ml)[10].

AZT has been found to inhibit haemoglobin synthesis and globin gene transcription[11]. AZT specifically inhibits beta-globin gene expression in human erythroid progenitors leading to marked cell growth inhibition at clinically relevant concentrations (1mM)[12] Toxic metabolites may also be relevant for cytotoxicity. A toxic metabolite of AZT, 3'-amino-3'-deoxythymidine (AMT), has been observed in cultured hepatocytes and microsomes which is toxic to bone marrow cells, particularly erythroid lines[11,13]. A role may also be played by the incorporation of AZT-MP into the nuclear DNA of these erythrocyte progenitors cells[14] and by down regulation of erythropoietin receptors[15]. Mitochondrial toxicity has also been suggested to contribute, as incubation of the Friend murine erythroleukemic cell line with AZT (at the physiologic exposure of 5 mM) for several days leads to a decrease in the rate of cell growth, inhibition of mtDNA replication, reduction of mtDNA per cell and per mitochondrion, and changes in lactate and ATP synthesis and in oxygen uptake, suggesting impairment of oxidative phosphorylation[16].

Both AZT and d4T lead to macrocytosis but only AZT causes anaemia. The reasons for this difference is not clear. Bone marrow cell lineages are markedly more sensitive to AZT as compared with other nucleoside analogs. Supplementation with vitamin B12 or folate do not prevent AZT related macrocytosis, anaemia or neuropenia[17] although a beneficial effect in certain subgroups of patients cannot be excluded. Vitamin E, zinc, N-acetylcysteine (NAC) and lithium all may have some protective effects against this toxicity but have not been extensively studied *in vivo*[18-20].

Addition of 3TC may marginally increase the anaemia risk with AZT, precipitous drops in haemoglobin after the introduction of 3TC to ongoing AZT therapy has been reported[21]. Combination of ddI with AZT was not associated with an increased risk of haematological toxicity relative to AZT alone in two large randomised studies[22,23].

Anaemia - Morbidity and Mortality in HIV infection

Anaemia is an independent risk factor for disease progression and death in persons with HIV infection. Even modest (1 g/dl) changes in haemoglobin may associate with a significant increased risk of death (Table 3). These associations appear consistent across a range of populations and in both the pre-therapy, pre-HAART and HAART eras. Additionally, as these associations are independent of antiretroviral therapy and effective virological control it is possible that the mechanism of anaemia is less important than the presence of anaemia per se in affecting prognosis. This may be particularly relevant in drug choice for individuals at greatest risk of

Table 2. *Myleosuppressive drugs, by therapeutic class, commonly used in the setting of HIV infection.*

Antineoplastics	Anti-infectives	Antivirals
Cyclophosphamide	Dapsone	Cidofovir
Doxyrubicin	Pyramethamine	Foscarnet
Etoposide	Sulphonamides	Ganciclovir
Hydroxyurea	Trimethroprim	Interferon α,
		Ribavirin
		Zidovudine and
		possibly Lamivudine

Table 3. *Increase in risk of death per 1 g/dl reduction in haemoglobin.*

Study	Increase in risk of death (95% confidence intervals, p value)	Reference
Concorde	1.41 (1.33-1.52) <0.001	[44]
EuroSida	1.57 (1.41-1.75) <0.001	[25]
Chene G	1.14 (1.09-1.18) <0.01	[45]

anaemia and underlines the need for early intervention when haemoglobin declines.

Independent association of anaemia with disease progression generally does not associate with specific disease events, although in the MACs study anaemia and dementia were linked[24]. It is important to note that associations derived from cohort studies do not indicate causative relationships. Anaemia may, in many individuals, simply be a marker of poor health or of an impending infection or tumour event that is otherwise presently sub-clinical.

Several of the studies provide information of specific practical interest to the practising physician and are therefore highlighted here. In the Multistate Adult and Adolescent Spectrum of HIV Disease Surveillance Project[2] case records of 32,867 patients who received HIV care in hospitals and clinics in nine US cities were studied. In all, 7261 anaemic patients were included in the mortality analysis. Anaemia was associated with increased risk of death but also treatment of anaemia, either with transfusion or rHuEPO, to attain a rise in Hb of 1g/dl or increase Hb from <10 to >10g/dl improved survival. These observations remained true when correction for CD4 cell count was performed. For example, the relative risk of death in individuals whose baseline CD4 count was ≥200 cells/mm^3 was 148% higher in anaemic individuals compared to non-anaemic individuals. Patients who recovered from anaemia when their baseline CD4 count was ≥200 cells/ mm^3 survived 28 months longer than patients who did not recover. Factors significantly associated with anaemia included the presence of any opportunistic disease, particularly lymphoma and bacterial septicaemia, female sex, African-American ethnicity, and the use of myelosuppressive medications such as AZT or ganciclovir whereas age or mode of HIV acquisition were not associated with anaemia[2].

In the EuroSIDA cohort[25], anaemia was an independent predictive marker of prognosis in 6725 prospectively followed patients. Anaemia was remarkably common with only 40.4% of patients having a normal Hb (defined as >14 g/dl for men, >12 g/dl for women). Mild anaemia (>8 g/dl but < normal values) was present in 58.2% and severe anaemia (<8 g/dl) in 1.4% of patients at recruitment. The proportion of patients estimated to have died after 12 months was 3.1% of patients without anaemia, 15.9% of patients with mild anaemia, and 40.8% of patients with severe anaemia. Anaemia was a strong independent risk factor for death in the multivariate, time adjusted Cox proportional hazards model even after adjusting for demographic factors, AIDS and antiretroviral treatment. For every 1 g/dL decrease in Hb there was a 57% increase in the hazard of death. CD4 and HIV RNA levels were also predictive of the risk of death. Patients whose CD4 count was reduced by 50% and patients who had a 1 log^{10} increase in viral load had a 51 and 37% increased risk of death, respectively[25]. In other words, anaemia was a stronger predictor of risk than either of these well established disease markers.

Given the association between female sex and anaemia, several studies have focused specifically on female populations. The prevalence of anaemia is higher in HIV-positive (28.1-37%) relative to HIV-negative women (15.1-17%)[26,27]. Both the Women's Interagency HIV Study[26] and Human Immunodeficiency Virus Epidemiology Research Study Group (HER)[27] have shown the development of anaemia (Hb <12 g/dL) is most common in African-American women, the risk being increased over 2-fold relative to women of other ethnicities. In the Women's Interagency HIV Study anaemia was also more likely to occur in HIV-infected women who had a CD4 count <200 cells/mm^3, higher plasma HIV RNA level, history of an AIDS-defining condition, and in those currently taking AZT or have had a history of taking AZT within the prior 6 months. The use of nucleoside analogs other than AZT was not statistically associated with anaemia (Table 4)[26]. The HER study had remarkably similar findings, age (per 5-year increase), lower body mass index, history of pneumonia, oral candidiasis or fever, CD4 <200/mm^3 and AZT use all increased the risk of anaemia significantly. Of note, however, the significance of some of these factors was lost when patients treated in the HAART era (1996-2000) were examined. Specifically, pneumonia, fever and AZT use all lost significance[27].

A recent cohort analysis from Johns Hopkins suggested that the use AZT was not a significant risk factor for anaemia in HAART treated patients. In this analysis of 905 patients receiving care at Johns Hopkins since July 1996 only 21% of patients starting HAART had a Hb >14g/dl but after 1 year of therapy 42% of individuals had Hb >14g/dl, this benefit being regardless of AZT use. Anaemia was significantly more likely to recover if HAART was given compared with untreated persons[28]. However, data from prospective randomised studies suggest that anaemia events remain more common with AZT-based HAART relative to d4T-based therapy. In the START 1&2 studies, indinavir-based HAART reg-

Table 4. *Association between AZT treatment and anemia (Hb <12 g/dL) in women with HIV infection[26].*

CD4 count (cells/mm^3)	Patients with Anemia (%) on AZT-based Regimen	Patients with Anemia (%) on AZT-sparing Regimen	Untreated Patients with anemia (%)	*P Value*
0-199	57.2	49.1	61.9	.06
200-499	32.8	24.3	30.0	NS
500+	36.7	28.6	20.2	<.05
Total	41.6	38.7	34.3	<.01

imens were compared by nucleoside backbone. In the AZT-3TC treated patients (n=206 randomised) Hb<12 g/dl occurred in 16% of patients compared with 9% in d4T treated patients (n=203 randomised, 101 with 3TC, 102 with ddI) amongst individuals with Hb >12 g/dl at baseline (p=0.046). Mean Hb fell in the AZT group but rose with d4T over 48 weeks treatment. Grade 3-4 anaemia (i.e. Hb <8 g/dl) occurred in 1.5% of AZT but 0% of d4T treated patients. Grade 3-4 neutropenia was also more common with AZT (32%) relative to d4T-regimens (15%) ($p < 0.001$)[29-31]. These studies did not specifically evaluate whether specific baseline demographic characteristics were associated with an increased risk of anaemia.

Taking cohort and clinical trials data together, the impression would be that whilst Hb improves overall with HAART, possibly through a reduction in infection and chronic disease related anaemia, thymidine analog choice continues to play a role in the risk of haematological complications.

Anaemia and Quality of life

Anaemia, even at grade 1 severity has been shown in patients with renal disease as well as in patients with malignancies undergoing chemotherapy to impact quality of life[1]. The symptoms of anaemia depend on various factors, including the severity grade, the rapidity of onset, and the age and physiologic status of the patient. The symptoms experienced by patients vary from coldness, dizziness, and palpitations to pulmonary oedema, cardiac failure, depression, and impairment of cognitive function. Fatigue is perhaps the most important dimension of mild anaemia. Fatigue is a common complaint of patients with malignancies and HIV resulting in significant disability and adverse effects on quality of life[32]. Its aetiology remains unclear and is most likely multifactorial. Despite its impact and prevalence, fatigue is often overlooked and undertreated in these patient populations. Fatigue is general perceived as being of indeterminable aetiology and largely untreatable. Anaemia represents one of the few clearly treatable causes of fatigue and may act as a pointer to other contributors to fatigue such as nutritional deficiencies[33]. In the setting of HIV infection, two studies have reported on the benefits of anaemia treatment with rHuEPO and quality of life. The treatment of anaemia (defined in one study as Hb ≤11 g/dl, the other study as haematocrit <30) with erythropoietin led to a mean 2.5 g/dl increase in Hb[34] or a rise in mean haematocrit to >33[35] and was associated with quality of life improvements that were independent of changes in CD4 count and baseline anaemia severity. Dimensions of function and physical well being were both improved, most notably energy improved[34,35].

The recognition and treatment of anaemia, including mild anaemia, therefore leads to improvements in both quality and length of life for persons with HIV infection. Avoiding the development of anaemia in persons with HIV infection will contribute to maintenance of quality of life and probably an improved clinical outcome.

Management of Anaemia

Prevention

Prevention of anaemia should be the mainstay of management. As studies have identified that patients with CD4 cell counts <200/mm^3 and opportunistic disease are at increased risk, intervention with HAART along current treatment guidelines (i.e. before CD4 falls below 200/mm^3) should reduce the risk of an individual developing anaemia. Additionally, women and those of African (or African-American) origin are also at greater risk. As randomised clinical trials in the HAART era have demonstrated that differences in anaemia risk exists between thymidine analogs it may be appropriate to consider regimens that do not contain AZT in these individuals, any person who presents with low haemoglobin and individuals requiring other myelosuppressive agents. Additionally, dietary advice to optimise nutrient intake, correction of nutritional deficiencies and to provide guidance in heart healthy eating should be initiated at presentation with HIV infection.

Elimination of causation

Once anaemia develops intervention is appropriate as it may both improve quality of life and reduce morbidity and mortality. The level at which a persons should be defined as anaemic is arbitrary and may in part be based on the presence of symptoms such as fatigue or diminished physical function. Quality of life is improved with intervention when Hb is <11 g/dl[34] so this may be an appropriate level. A recent consensus statement has suggested that Hb <12 g/dl in men and <11 g/dl in women are levels where intervention should be considered[3]. Clearly, a low haemoglobin value should be confirmed before intervention is considered. The short-term risks of anaemia may be greatest in individuals with other health problems most notably cardiac and renal disease therefore these individuals may require early intervention.

The investigation of anaemia in HIV infection follows along the same lines as in general medicine and should routinely include drug history, enquiry about blood loss particularly in stools, urine, or via menorrhagia, evaluation of vitamin B12, folate and iron stores, as well as investigation for parvovirus B19 and if the CD4 is <200/mm^3 for other infections such as *Mycobacterium avium* or *Cryptococcus neoformans.* Assessment of erythropoietin levels may be appropriate if intervention with this agent is being considered and may be useful in assessing whether anaemia is related to AZT (where levels are generally normal or elevated) or chronic disease (where levels may be low).

Interventions for anaemia are limited. Drug switching, to a regimen which does not contain AZT should be considered, but has not been specifically investigated in the HAART era. In the absence of clear evi-

dence of iron deficiency, iron supplementation should be avoided, as this may be associated with accelerated disease progression. Evidence for the risk of iron overload comes from several sources. Simultaneous administration of low doses of oral iron with dapsone for the prophylaxis of *Pneumocystis carinii* pneumonia in HIV-positive patients was associated with excess mortality relative to those receiving aerosolised pentamadine. A retrospective cohort study in thallasemia major patients found the rate of disease progression was significantly faster in patients receiving lower doses of iron-chelating desferrioxamine and higher serum ferritin concentrations. A study of haptoglobin polymorphisms in HIV-positive subjects indicated that the haptoglobin 2-2 polymorphism was associated with both higher iron stores and shortened survival as compared with the haptoglobin 1-1 or 2-1 phenotypes and a retrospective study of bone marrow macrophage iron in HIV-positive patients suggested that survival is shorter with high iron stores[5,36]. These studies were not conducted in the HAART era and we all performed in the developed world. Investigations in other settings are required to confirm these concerns are real and generally applicable. Supplementation with B12 and folate has not been suggested to be harmful but is not effective in the setting of AZT related anaemia[17].

Transfusion

Transfusion is the treatment of choice in acute or severe, symptomatic anaemia. However, transfusion carries risks for persons with HIV. Beyond the theoretical concerns regarding transmission of infections not routinely screen for by transfusion services, transfusion may contribute to the risk of iron overload and has been associated with increased risk of death in the pre-HAART era, independent of other factors including baseline anaemia[34]. It appears that blood transfusions may directly activate of HIV expression and trigger transfusion related immunosuppression. HIV viral load has been noted to rise following blood transfusion[4,38]. Studies evaluating viral activity after transfusion in patients with suppressed viral load on HAART have not been reported.

Recombinant human erythropoietin

Recombinant human erythropoietin (rHuEPO) is the mainstay of treatment for anaemia. The evidence for effectiveness of this agent, at least at a dose of 100 U/kg thrice weekly by intravenous bolus, is limited to persons with endogenous erythropoietin levels ≤500 IU/L[6,39-41]. Above this level benefit has not been demonstrated. As individuals with AZT related anaemia may have erythropoietin levels ranging from 9-3,390 mU/ml[10] it is clear that rHuEPO will not be suitable for all patients. Therefore, measurement of endogenous erythropoietin levels should be performed prior to initiation of rHuEPO treatment. Erythropoietin, administered as 100-300 units/kg subcutaneously 3 times a week, has been demonstrated to increase haemoglobin levels by 2.5 g/dl over a 4 month period in 221 patients with HIV-infection and Hb <11 g/dl[34]. A second study of 251 anaemic patients (defined as hematocrit <30%) with AIDS and serum erythropoietin level ≤500 IU/L used an initial rHuEPO dosage of 4,000 units subcutaneously for 6 days each week. Based on the patient's response to therapy, the dosage was increased sequentially to 8,000 units subcutaneously for 6 days per week. Changes in mean hematocrit level from a baseline of 27.9% to 33.6% were observed at week 12 ($p < .0001$) and to 34.5% at week 24 ($p < .0001$)[35]. Quality of life improvements were demonstrated in both these studies most notably in terms of energy and physical functioning[34,35]. Additionally, rHuEPO reduces transfusion requirements in HIV-infected patients who have endogenous erythropoietin levels of ≤500 U/L[6,39].

Therapy with rHuEPO is generally well tolerated with adverse events rates similar to placebo injections[6]. Current recommendations for rHuEPO use in persons with endogenous erythropoietin <500 U/ml are to initiate with 100-300 U/kg subcutaneously thrice weekly with the aim to increase Hb by 1 g/dl by week 4. Once weekly dosing of rHuEPO is under consideration. Higher doses, up to 60,000 U/week, of rHuEPO can be considered if a satifactory response is not observed. Once Hb has reached 13 g/dl rHuEPO can be discontinued and resumed once Hb falls below 12 g/dl[3]. These expert opinion-based guidelines encourage more aggressive treatment of anaemia than is currently routine in clinical practice and are likely to, in part, reflect the authors' appreciation from clinical trials experience of the quality of life benefits that treatment of anaemia brings.

The main obstacle to the prescription of rHuEPO is cost. Cost effectiveness studies in a range of disease areas including HIV-infected children (but not adults) suggest the drug costs may readily be offset against transfusion costs[42]. As rHuEPO treatment improves quality of life in HIV and treatment of anaemia in HIV is associated with improved survival analysis of cost per quality adjusted life years (QALYs) saved would be feasible in HIV. However such an analysis has not been reported to date. In cancer-associated anaemia, where rHuEPO improves quality of life but generally not survival, rHuEPO is cost effective. Estimates from a range of case based scenarios with varying assumptions are that the effectiveness resulting from $US 1 spent on standard care can be achieved with only $US 0.81 of rHuEPO care[43]. That is to say, all costs considered rHuEPO may actually save the healthcare budget money.

Conclusions

Anaemia impacts quality of life and survival in persons with HIV infection. HAART is effective in reducing the risk of anaemia and enabling low haemoglobin to recover although clinical trials data indicate that differences in the effects of HAART on anaemia exist between AZT- and d4T-based regimens. The relative risks of thymidine analog-spar-

ing regimens have not been assessed. In randomised clinical trials of HAART therapy, AZT use continues to be associated with anaemia and a decline in Hb over 48 weeks follow-up. Other risks for anaemia include the presence of opportunistic disease, CD4 cell count <200/mm^3, female sex and African (or African-American) origin. These individuals and others presenting with anaemia may require additional monitoring during therapy and should probably avoid AZT therapy if feasible. Treatment for anaemia includes identification and management of the cause, transfusion and rHuEPO. Treatment even of relatively mild anaemia (Hb <11 g/dl) leads to improvements in quality of life and resolution of anaemia is associated with improved survival. Recent consensus guidelines[3], which underline the considerable impact of anaemia on quality of life, suggest that intervention for anaemia should be considered in men with Hb <12 g/dl and women with Hb <11g/dl.

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References

1. Ludwig H, Strasser K. Symptomatology of anemia. Semin Oncol 2001;28(Suppl 8):7-14
2. Sullivan P, Hanson D, Chu S, et al. Epidemiology of anaemia in HIV-infected persons: Results from the Multistate Adult and Adolescent Spectrum of HIV Disease Surveillance Project. Blood 1998;91:301-8
3. Volberding P. Consensus statement: anemia in HIV infection—current trends, treatment options, and practice strategies. Anemia in HIV Working Group. Clin Ther 2000;22:1004-20
4. Groopman J. Impact of transfusion on viral load in human immunodeficiency virus infection. Semin Hematol 1997;34(Suppl 2):27-33
5. Gordeuk V, Delanghe J, Langlois M, Boelaert J. Iron status and the outcome of HIV infection: an overview. J Clin Virol 2001;20:111-5
6. Henry D, Beall G, Benson C, et al. Recombinant human erythropoietin in the treatment of anemia associated with HIV infection and zidovudine therapy. Overview of four clinical trials. Ann Intern Med 1992;117:739-48
7. De Marchi S, Pirisi M, Ferraccioli G. Erythropoietin and the anemia of chronic diseases. Clin Exp Rheumatol 1993;11:429-44.
8. Means R Jr. Cytokines and anaemia in HIV infection. Cytokines Cell Mol Ther 1997;3:179-86
9. Walker R, Parker R, Kovacs J, et al. Anemia and erythropoiesis in patients with the acquired immunodeficiency syndrome (AIDS) and Kaposi sarcoma treated with zidovudine. Ann Intern Med 1988;108:372-6
10. Rarick M, Loureiro C, Groshen S, et al. Serum erythropoietin titers in patients with HIV infection and anemia. J Acquir Immune Defic Syndr 1991;4:593-7
11. Weidner D, Bridges E, Cretton E, Sommadossi J. Comparative effects of 3'-azido-3'-deoxythymidine and its metabolite 3'-amino-3'-deoxythymidine on hemoglobin synthesis in K-562 human leukemia cells. Mol Pharmacol 1992;41:252-8
12. Spiga M, Weidner D, Trentesaux C, LeBoeuf R, Sommadossi J. Inhibition of beta-globin gene expression by 3'-azido-3'-deoxythymidine in human erythroid progenitor cells. Antiviral Res 1999;44:167-77
13. Cretton E, Xie M, Bevan R, Goudgaon N, Schinazi R, Sommadossi J. Catabolism of 3'-azido-3'-deoxythymidine in hepatocytes and liver microsomes, with evidence of formation of 3'-amino-3'-deoxythymidine, a highly toxic catabolite for human bone marrow cells. Mol Pharmacol 1991;39:258-66.
14. Sommadossi J, Carlisle R, Zhou Z. Cellular pharmacology of 3'-azido-3'-deoxythymidine with evidence of incorporation into DNA of human bone marrow cells. Mol Pharmacol 1989;36:9-14.
15. Gogu S, Beckman B, Wilson R, Agrawal K. Inhibitory effects of zidovudine in erythroid progenitor cells. Reversal with a combination of erythropoietin and interleukin-3. Biochem Pharmacol 1995;50:413-9.
16. Hobbs G, Keilbaugh S, Rief P, Simpson M. Cellular targets of 3'-azido-3'-deoxythymidine: an early (non-delayed) effect on oxidative phosphorylation. Biochem Pharmacol 1995;50:381-90.
17. Falguera M, Perez-Mur J, Puig T, Cao G. Study of the role of vitamin B12 and folinic acid supplementation in preventing hematologic toxicity of zidovudine. Eur J Haematol 1995;55:97-102.
18. Gogu S, Lertora J, George W, Hyslop N, Agrawal K. Protection of zidovudine-induced toxicity against murine erythroid progenitor cells by vitamin E. Exp Hematol 1991;19:649-52.
19. Gogu S, Agrawal K. The protective role of zinc and N-acetylcysteine in modulating zidovudine induced hematopoietic toxicity. Life Sci. 1996;59:1323-9.
20. Gallicchio V, Hughes N, Tse K. Modulation of the haematopoietic toxicity associated with zidovudine in vivo with lithium carbonate. J Intern Med 1993;233:259-68.
21. Tseng A, Conly J, Fletcher D, Keystone D, Salit I, Walmsley S. Precipitous declines in hemoglobin levels associated with combination zidovudine and lamivudine therapy. Clin Infect Dis 1998;27:908-9.
22. Delta Coordinating Committee. Delta: a randomised double-blind controlled trial comparing combinations of zidovudine plus didanosine or zalcitabine with zidovudine alone in HIV-infected individuals. Lancet 1996;348:283-91.
23. Hammer S, Katzenstein D, Hughes M, et al. A trial comparing nucleoside monotherapy with combination therapy in HIV-infected adults with CD4 cell counts from 200 to 500 per cubic millimeter. AIDS Clinical Trials Group Study 175 Study Team. N Engl J Med 1996;335:1081-90.
24. McArthur J, Hoover D, Bacellar H, et al. Dementia in AIDS patients: incidence and risk factors. Neurology 1993;43: 2245-52.
25. Mocroft A, Kirk O, Barton S, et al. Anaemia is an independent predictive marker for clinical prognosis in HIV-infected patients from across Europe. EuroSIDA study group. AIDS 1999; 13:943-50.
26. Levine A, Berhane K, Masri-Lavine L, et al. Prevalence and correlates of anaemia in a large cohort of HIV-infected women. Women's interagency HIV study. J Acquired Immune Defic Syndr 2001;28:26:8.
27. Semba R, Shah N, Klein R, et al. Prevalence and cumulative incidence of and risk factors for anaemia in a multicenter cohort study of HIV-infected and –uninfected women. Clin Infect Dis 2002;34:260-6.
28. Moore R, Forney D. Anaemia in HIV-infected patients receiving highly active antiretroviral therapy. J Acquire Immune Defic Syndr 2002;29:54-57.
29. Squires K, Gulick R, Tebas P, et al. A comparison of stavudine plus lamivudine verus zidovudine plus lamivudine in combination with indinavir in antiretroviral naïve individuals with HIV infection: selection of thymidine analog regimen therapy (START I). AIDS 2000;14:1591-600.
30. Eron J Jr, Murphy R, Peterson D, et al. A comparison of stavudine, didanosine and indinavir with zidovudine, lamivudine and indinavir for the initial treatment of HIV-1 infected individuals: selection of thymidine analog regimen therapy (START II). AIDS 2000;14:1601-10.
31. Pavia A, Olson J, Mauney J, Wills B. Differences in hematological complications in the selection of thymidine analog regimen therapy trials (START I and START II). 13th World AIDS Conference, Barcelona, July 2002 (in press).
32. Groopman J. Fatigue in cancer and HIV/AIDS Oncology 1998;12:335-44.
33. Sobrero A, Puglisi F, Guglielmi A. Fatigue: a main component of anemia symptomatology. Semin Oncol 2001;28(Suppl 8):15-8.

34. Abrams D, Steinhart C, Frascino R. Epoetin alfa therapy for anaemia in HIV-infected patients: impact on quality of life. Int J STD AIDS 2000;11:659-65.
35. Revicki D, Brown R, Henry D, McNeill M, Rios A, Watson T. Recombinant human erythropoietin and health-related quality of life of AIDS patients with anemia. J Acquir Immune Defic Syndr 1994;7:474-84.
36. Clark T, Semba R. Iron supplementation during HIV infection: a double-edged sword? Med Hypotheses 2001;57:476-9.
37. Moore R, Keruly J, Chaisson R. Anaemia and survival in HIV infection. J Acquire Immune Defic Syndr 1998;19:29-33.
38. Mudido P, Georges D, Dorazio D, et al. HIV type 1 activation after blood transfusion. Transfusion 1996;36:860-5.
39. Fischl M, Galpin J, Levine J, et al. Recombinant human erythropoietin for patients with AIDS treated with zidovudine. N Engl J Med 1990;322:1488-93.
40. Phair J, Abels R, McNeill M, Sullivan D. Recombinant human erythropoietin treatment: investigational new drug protocol for the anemia of the acquired immunodeficiency syndrome. Overall results. Arch Intern Med 1993;153:2669-75.
41. Henry D, Jemsek J, Levin A, et al. Recombinant human erythropoietin and the treatment of anemia in patients with AIDS or advanced ARC not receiving ZDV. J Acquir Immune Defic Syndr 1992;5:847-8.
42. Allen U, Kirby M, Goeree R. Cost-effectiveness of recombinant human erythropoietin versus transfusions in the treatment of zidovudine-related anemia in HIV-infected children. Pediatr AIDS HIV Infect 1997;8:4-11.
43. Cremieux P, Finkelstein S, Berndt E, Crawford J, Slavin M. Cost effectiveness, quality-adjusted life-years and supportive care. Recombinant human erythropoietin as a treatment of cancer-associated anaemia. Pharmacoeconomics 1999; 16:459-72.
44. Walker A, Peto T, Babiker A, Darbyshire J. Markers of HIV infection in the Concorde trial. Concorde Co-ordinating Committee. QJM 1998;91:423-38.
45. Chene G, Easterbrook P, Juszczak E, Yu L, Pocock S, Gazzard B. Long-term survival in patients with advanced immunodeficiency. AIDS 1997;11:209-16.