Use of Hematopoietic Hormones for Bone Marrow Defects in AIDS

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Bone marrow suppression is a substantial problem in patients infected with HIV. Contributing factors include the underlying HIV infection, alterations in the marrow microenvironment (resulting in abnormal cytokine regulation

Introduction

Hematopoietic hormones are being used increasingly in clinical practice, most often to maintain the dose intensity of conventional chemotherapy schedules, decrease the risk of neutropenic fever, and reduce the period of neutropenia or anemia following high-dose chemotherapy plus bone marrow transplantation and chemotherapy protocols for leukemia.[1] Hematopoietic growth factors are also frequently employed in the setting of active infections, including AIDS, either to ameliorate the myelosuppressive toxicities of various antibiotics and chemotherapy regimens or to augment the host immune response.[2,3] Clinicians use these drugs to control the number and function of host defense cells but are uncertain as to the specific settings in which they are most useful.[4,5]

This review briefly outlines the bone marrow defects that occur during various stages of HIV infection, as well as some pathophysiologic mechanisms that may contribute to alterations in hematopoiesis. The expanding literature on the use of hematopoietic growth factors in the treatment of AIDS is then discussed, with particular focus on the three colony-stimulating factors (CSFs) most commonly used clinically: recombinant human erythropoietin (rHuEPO [Epopogen, Procrit]), granulocyte-macrophage colony-stimulating factor (GM-CSF, sargramostim [Leukine, Prokine]), and granulocyte-colony stimulating factor (G-CSF, filgrastimostim [Neupogen]).

Bone Marrow Defects in HIV

The immunopathogenesis of HIV infection is extremely complex. A variety of viral and immune mechanisms contribute to the progressive deterioration of immunologic function and to the progression of HIV disease to AIDS.[6] By weakening the host’s immune system, the virus indirectly contributes to his or her likelihood of contracting opportunistic infections and malignancies, which are the clinical hallmarks of this devastating illness.

Cytopenias occur in 10% to 20% of individuals with early HIV disease and in 75% to 90% of those with advanced disease.[7] Ineffective hematopoiesis and premature destruction of circulating blood cells (due to autoimmunity and a menagerie of viral, bacterial, fungal, and protozoan infections) are additional contributing factors. Opportunistic malignancies and the myelosuppressive effects of antiviral, antimicrobial, and chemotherapeutic agents further compromise the host’s ability to maintain adequate blood counts. The precise mechanisms that result in ineffective hematopoiesis are poorly defined and usually multifactorial (Table 1).

Histologic Marrow Alterations With HIV Infection

In 50% to 60% of patients with AIDS, bone marrow is hypercellular, due to absolute hyperplasia in one or more of the nonlymphoid cell lines.[8,9] In general, the myeloid-to-erythroid ratio tends to be close to normal or shows a relative myeloid hyperplasia.[7] Lymphoid aggregates, plasmacytosis, and dysplasia are often noted, although their reported frequencies vary considerably in different reviews. This variation is due, in large part, to the failure of these retrospective studies to take into account such confounding clinical variables as the stage of HIV disease, coexisting infection, and drug therapies. Approximately 5% of patients have hypocellular bone marrow, typically in the setting of advanced HIV infection.

A dysplasia of at least one cell line occurs in approximately 70% of patients with AIDS.[10] The most common bone marrow features are dysplastic granulocytic maturation and vacuolization of granulocytic precursors. Roughly one-half of patients have erythrocytic dysplasia and one-third have
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megakaryocytic dysplasia.[11] Although the dysplasia is morphologically similar to that seen in primary myelodysplastic syndromes and is often associated with reticuloendothelial iron blockade and megaloblastic hematopoiesis, cytogenetic abnormalities and leukemic transformation rarely occur.[12] In general, the degree and frequency of dysplastic changes increase with concurrent opportunistic infections.[13]

Less certain is the relationship between peripheral blood cytopenias and the degree of marrow cellularity.[13,14] For example, the majority of patients with isolated thrombocytopenia have normal or increased marrow megakaryocytes with variable dysplastic features, as well as clinical findings suggestive of autoimmune idiopathic thrombocytopenia.[15] They may also have elevated levels of platelet-bound immunoglobulin and circulating immune complexes capable of binding platelets, and these abnormalities, more than a relative decrease in megakaryocyte production, contribute to the development of thrombocytopenia.[16]

Hematopoietic Alterations Due to Infection, Medications, or Tumor

Viral Infections—Several viruses may affect bone marrow function and diminish blood counts. The increased prevalence and pathogenicity of cytomegalovirus (CMV) infection in the immunocompromised host is particularly important. Like HIV, CMV may cause histiocytic erythrophagocytosis and autoimmune destruction of blood cells, but neither virus produces distinctive histopathologic changes in bone marrow.[17] Hematopoietic cells infected with CMV are less responsive to CSFs and may serve as reservoirs of latent viral infection.[18] Furthermore, CMV (and possibly HIV) can infect bone marrow stromal cells, potentially diminishing their ability to produce cytokines and growth factors.[19]

Parvovirus is a remediable cause of severe chronic anemia in patients with HIV infection.[20,21] Failure of erythrocyte production results from direct viral infection and lysis of erythroid progenitor cells. Although usually a self-limited illness, in the absence of an adequate antibody response, B19 parvovirus infection can persist. It may also rarely inhibit myeloid and megakaryocytic progenitors, resulting in neutropenia and thrombocytopenia.[22]

Pathognomonic histopathologic findings of parvovirus infection consist of giant pronormoblasts in the bone marrow together with an absence of erythroid progenitors.[20] The diagnosis can be confirmed by in situ hybridization, using sequence-specific parvovirus DNA probes.

Exposure to human herpesvirus-6 during infancy typically results in a mild, self-limited exanthem. The virus has a tropism for CD4+ lymphocytes and monocytes, where it may remain dormant for decades. With immunosuppression, it may reactivate and affect the ability of marrow precursor cells to respond to hematopoietic stimulants, resulting in further suppression of T-cell function.[23] The various hepatitis viruses may also downregulate hematopoiesis, although the mechanism by which they do so is less well understood.

Other opportunistic infections that can involve the bone marrow include fungi and mycobacteria.[24] Cryptococcus neofor mans, Histoplasma capsulatum, and Mycobacterium avium intracellulare (MAI) are the pathogens most likely to affect hematopoiesis.[7,8,12] In contrast, extrapulmonary pneumocystosis rarely involves bone marrow in the current era of effective systemic therapies to prevent Pneumocystis carinii pneumonia.[25,26] Occasionally, the host marrow may reveal disseminated fungal or mycobacterial involvement long before other signs of infection are apparent. Histologic clues suggesting fungal or mycobacterial infection include a marrow diffusely infiltrated with lymphoid and plasma cells that have loose macrophage aggregates and clusters. Less frequently seen are pseudogranuloma cells and granulomata.[7,24] Successful detection of these organisms requires the use of special stains, sensitive culture techniques, and patience. Weeks may pass before a fastidious pathogen is identified.

Examining the buffy coat may also demonstrate Histoplasma, Candida, or other phagocytized pathogens within the cytoplasm of neutrophils and monocytes. Many microbiology laboratories now employ lysis centrifugation techniques whereby white blood cells are lysed and intracellular pathogens are more rapidly released into culture media, reducing the time to obtain a positive culture.

Anti-infective Drugs—Drugs used to prevent and treat the infectious complications of AIDS are also hematotoxic. Of these, zidovudine (AZT [Retrovir]), cidofovir, pentamidine, trimethoprim-sulfamethoxazole, pyrimethamine (Daraprim), sulfadiazine, dapsone (Dapsone), amphotericin B, and, especially, ganciclovir (Cytovene), are the most problematic.

Myelosuppression is the most common dose-limiting toxicity of ganciclovir therapy (both oral and intravenous forms) in immunocompromised hosts. Dose-limiting neutropenia (minimal absolute neutrophil count [ANC] less than 500 cells/mm³) occurred in 24% of AIDS patients receiving chronic
oral ganciclovir for CMV retinitis, and anemia (minimal hemoglobin value less than 8.0 g/dL) developed in 15%; when ganciclovir was given intravenously, 37% of patients developed neutropenia and 24% became anemic.[27]

The hematologic side effects of many of these anti-infective drugs are amplified when they are used in varying combinations. Substituting less hematotoxic alternatives for the offending agent(s) can sometimes be accomplished without compromising treatment benefits.

Neoplasms are a common consequence of altered immunity. Non-Hodgkin’s lymphoma (NHL) will eventually develop in 10% to 15% of HIV-infected patients.[28] This percentage will likely increase as strategies to eliminate HIV viral replication and prevent and treat opportunistic infections improve. In this setting, lymphomatous bone marrow involvement is characterized by peripheral blood pancytopenia.[21] Obtaining a bone marrow aspirate and biopsy as part of the staging evaluation provides insight into the myeloid reserve, and possibly, the need for prophylactic intrathecal central nervous system therapy prior to beginning systemic chemotherapy.[29] Although not tested prospectively, retrospective studies suggest that patients at greatest risk for meningeal relapse are those with bone marrow involvement, sites of disease that are at close proximity to the meninges, or small noncleaved histology.[30]

Kaposi’s sarcoma has occurred in as many as 20% to 40% of HIV-infected adult homosexuals. However, the frequency of this complication in the United States is decreasing. Kaposi’s sarcoma rarely involves the bone marrow, although the drugs used to treat it are myelosuppressive. Interferon-alfa (Intron A, Roferon-A), vindesine (Eldisine), doxorubicin, etoposide (VePesid), and paclitaxel (Taxol) are associated with considerable hematologic toxicity, particularly if they are combined with other myelosuppressive drugs. Vincristine, bleomycin (Blenoxane),[31] and the newly available liposomal anthracyclines (Doxil and DaunoXome)[32,33] are generally less hematotoxic.

Mechanisms for Hematopoietic Dysfunction in HIV Infection

Marrow recovery is often delayed in AIDS patients exposed to myelosuppressive agents, suggesting either that the progenitor- or stem-cell pools do not respond to appropriate growth factor signals or that the on-demand production of growth factors is inadequate. Investigators have struggled to address this issue more fully, and the literature remains difficult to interpret. Several reports contain conflicting results, and many of these discrepancies probably are due to variations in performing read-out assays, particularly colony-forming unit assays; the varying sensitivity of the assays used to identify the presence of HIV genomic components; and differences in the patient populations studied.[34]

The role of HIV in causing hematopoietic abnormalities remains elusive, but two potential mechanisms are often cited.

Direct Infection of Progenitor and Stem Cells—First, HIV may directly infect stem cells and committed hematopoietic progenitor cells, inhibiting their growth and differentiation. Supporting this view is the observation that colony-forming capacity is reduced when unfractionated human bone marrow (or purified CD34+ cells obtained from normal human donors) is exposed to HIV.[35-39] However, this assertion is controversial.[40-43]

Indirect Effects on Bone Marrow Stroma—HIV may instead indirectly affect hematopoiesis by altering bone marrow stromal elements, either by inhibiting the production and release of growth factors or by inducing the release of mitotic inhibitors. CD34+ cells from most patients are not HIV-infected, suggesting that direct HIV infection of these cells is not essential for the hematopoietic suppression observed in infected individuals.[35,44]

Bone marrow stroma is a complex of many different cell types, including microvascular endothelial cells (MVECs), fibroblast macrophages, adipocytes, and reticular adventitial cells. Although the relative importance of bone marrow stroma in HIV disease is unknown, ultrastructural damage to these support cells occurs in patients with AIDS.[45] In vitro, HIV contributes directly to stromal abnormalities and concomitant hematopoietic dysfunction.[46,47]

In vivo, this has been more difficult to demonstrate, even though MVECs obtained from the brain, liver, and kidney are permissive to HIV infection. Recently, Moses and colleagues isolated bone marrow MVECs from normal volunteers and 11 HIV-seropositive patients. In bone marrow stromal cultures obtained from the HIV-infected subjects, MVECs were the predominant cells infected by HIV (5% to 20%).[34] Although HIV-infected stromal cultures enriched for MVECs constitutively expressed normal levels of interleukin-4 (IL-4), IL-6, G-CSF, GM-CSF, tumor necrosis factor-alpha, transforming growth factor, and steel factor, IL-alpha-induced release of IL-6 and G-CSF was significantly reduced.

In a complementary study, Mauss and colleagues measured endogenous serum G-CSF levels in HIV-seropositive individuals with afebrile neutropenia (ANC less than 1,000 cells/mm3) persisting for
at least 4 weeks. They found low serum CSF levels in these HIV-positive individuals, which were not
different from levels in nonneutropenic HIV-seropositive individuals or healthy volunteers but were
markedly lower than levels in afebrile neutropenic patients with acute leukemia.[48] Like Moses et
al, Mauss and associates contend that HIV infection of bone marrow MVECs reduces the capacity of
hematopoietic stroma to respond to regulatory signals that normally augment blood cell production
during periods of increased demand. This hypothesis may explain, in part, the neutropenia
frequently observed in patients with advanced HIV infection, both those who do and do not receive
myelotoxic antiretroviral therapy.

**Effects on Megakaryocytes and Macrophages**

Megakaryocytes may also be infected by HIV, and actual internalization of HIV has been observed by electron microscopy.[49,50] These megakaryocytes appear to be deficient in their ability to form platelets, and their presence is associated with thrombocytopenia. The newly identified megakaryocytic growth factor, thrombopoietin, has not yet been tested clinically in HIV-associated thrombocytopenia but holds
great promise for ameliorating the effects of chemotherapy-induced thrombocytopenia

Also worth considering is the importance of macrophages and dendritic cells in contributing to the various hematopoietic derangements seen with HIV infection. By secreting pro-inflammatory cytokines and hematopoietic growth factors, these cells play an essential role during an immune
response and in hematopoiesis. Their pleiotropic cytokines mediate inflammatory actions and link
the various components of the immune system.

Macrophages are also long-term reservoirs of HIV. Following HIV infection, dysregulation of their
various soluble mediators may further contribute to the pathogenesis of HIV-induced disease and
neutropenia.[51] For example, in one culture system, after macrophages from healthy donors were
infected with HIV, the release of pro-inflammatory mediators and hematopoietic growth factors were
then altered.[51] The secretion of tumor necrosis factor-alpha, IL-1-beta, IL-6, and IL-8 were
upregulated, and hematopoietic activity (reflected by decreased excretion of macrophage CSF
[M-CSF] and GM-CSF) was downregulated. In another system, recombinant HIV-tat protein stimulated
increased bone marrow macrophage production of transforming growth factor-beta-1, a potent
negative regulator of hematopoiesis.[52]

Finally, macrophages appear to release substances that increase the amount of an
apoptosis-triggering protein called FAS on the surface of CD4 T-cells. HIV-infected macrophages can
also trigger apoptosis in the brain's astrocytes and may contribute to the premature loss of primitive
hematopoietic progenitors by a similar mechanism.[53,54]

From these and other studies, it is apparent that hematopoiesis is a highly regulated process that
requires dynamic alterations in the production of soluble factors to stimulate or inhibit growth of
hematopoietic progenitor cells.[34-48,51-59] Mechanisms that may account for some HIV-associated
hematopoietic abnormalities are summarized in **Table 2**.

**HIV-Associated Anemia**

The incidence of anemia varies among individuals with HIV infection.[7,13,17] Approximately 15% of
asymptomatic patients have a mild reduction in hemoglobin of 0.5 to 2.0 g/dL. In those with
symptomatic disease, 15% to 40% are anemic, with a hemoglobin deficit of 1 to 2 g/dL. More severe
anemia is present in 75% to 90% of untreated patients with AIDS. As indicated in **Table 3**, many
potential causes contribute to this problem.

Before offering treatment recommendations to this medically diverse group, it is necessary to
evaluate the nature and severity of the anemia and to look for possible reversible causes. Decreased
iron, vitamin B12 or folate levels are rarely contributing factors, and yet consideration of these
potentially reversible etiologies is always warranted.[58]

Significant immune hemolytic anemia is distinctly uncommon, although patients may occasionally
exhibit red blood cell autoantibodies.[60] The detection of autoantibodies per se is not a not a reason
to treat unless immune-mediated hemolysis occurs, in which case it may respond to steroids,
immunoglobulin, or splenectomy. Very rarely, microangiopathic hemolytic anemia occurs secondary
to thrombotic thrombocytopenic purpura, and this, too, may be treated in a conventional fashion
with plasmapheresis.[61] Intravenous immunoglobulin (400 mg/kg/d over 5 to 10 days) may reverse
the giant pronormoblastic hypoproliferative anemia of parvovirus B19 infection.[20,21]

**Effects of Antiretrovirals**

Antiretrovirals used to treat HIV-infected patients may further aggravate the anemia of HIV infection.
One such drug, AZT, is associated with several side effects, the most important of which is bone
marrow suppression characterized by macrocytic anemia, leukopenia, and, occasionally,
In a representative controlled trial, 31.3% of AZT-treated patients had reductions in their hemoglobin levels to less than 7.5 g/dL, as compared with only 2.7% of those given placebo.[63] Severe neutropenia (ANC less than 500 cells/mm$^3$) developed in 16% of patients who received AZT. Only one patient's platelet count fell to less than 25,000 cells/mm$^3$, while in three, bone marrow hypoplasia occurred, which improved slowly after drug discontinuation.

As a thymidine analog, AZT acts primarily to terminate HIV-reverse-transcriptase activity. The drug may also impair normal hematopoiesis by inhibiting DNA polymerase and directly suppressing committed stem-cell growth of burst forming unit GM (BFU-GM) and BFU-erythroid (BFU-E) colonies.[64]

The other dideoxynucleoside analogs presently used as antiretroviral agents can also inhibit BFU-GM and BFU-E at sufficiently high doses.[17] However, at the doses most commonly used in clinical practice, these agents are associated with less severe hematologic toxicity, and can usually be substituted for AZT. These include ddC (zalcitabine [Hivid]), ddI (dideoxyinosine [Videx]), D4T ( stavudine [Zerit]), and 3TC (lamivudine).

The four currently available protease inhibitors, saquinavir (Invirase), ritonavir (Norvir), indinavir (Crixivan), and nelfinavir (Viracept), and two nonnucleoside reverse transcriptase inhibitors, nevirapine (Viramune) and delavirdine (Rescriptor), also produce mild hematologic toxicities. Combination antiretroviral therapy using nucleoside reverse transcriptase inhibitors in tandem with protease inhibitors and/or nonnucleoside reverse transcriptase inhibitors is revolutionizing the way we treat AIDS patients, although the relative merits, potential toxicities, and drug-drug interactions of the different combinations are not fully defined.[65]

Red Blood Cell Transfusions

Indications for blood transfusions vary among North America blood banks and the AIDS Clinical Trial Group (ACTG). Factors that increase the patient's likelihood of receiving blood include stage of AIDS, drugs that he or she is receiving, and underlying opportunistic infections.[66] In two large AZT-treated cohorts, 47%[62] and 31%[63] of patients required blood transfusions. The importance of opportunistic infections in increasing the need for blood transfusions is reflected by another study showing that patients with MAI bacteremia were 5.2 times more likely to receive red blood cell transfusions than those with negative blood cultures.[67]

Strategies designed to prevent MAI among those with CD4+ cell counts less than 75 cells/mm$^3$ may translate into a diminished need for red blood cell transfusions. In one retrospective analysis, AIDS patients who received rifabutin prophylaxis required fewer blood transfusions than their counterparts who did not receive MAI prophylaxis.[68]

Although seemingly a simple solution, there are a number of theoretical and practical reasons why managing anemia with transfusions may not represent an ideal strategy in already immunocompromised patients. Allogeneic transfusion affects the recipient's immunologic function, including reduced response in mixed lymphocyte culture, decreased cytokine production, decreased natural killer cell activity, decreased helper T-cell number, decreased monocyte function, and increased suppressor T-cell number.[66,69]

In addition to these immunologic perturbations, there are adverse clinical sequelae, including transmission of blood-borne and lymphotrophic infections (eg, babesiosis, malaria, human T-cell lymphotrophic virus I or II, CMV, and viral hepatitis) and, in those given numerous transfusions, iron overload.[70,71] Some studies of allogeneic blood recipients suggest an increased risk of preoperative infection and cancer recurrence,[69,72-74] although others contest these findings.[75,76]

Transfusions may pose special risks for HIV-infected patients, including virus activation with possible disease progression and de novo CMV infection or reinfection.[76] For example, Sloand and coworkers found that CMV infection, wasting, and bacterial infections were significantly increased in transfused patients.[77] The frequency of CMV infection was related to the number of units of blood received.

Such studies linking allogeneic blood components with adverse clinical outcomes in persons with HIV should, however, be viewed as preliminary. Other researchers have found only a weak association between survival of AIDS patients and red blood cell transfusions.[78]

Erythropoietin

Relative to their degree of anemia, AIDS patients have inappropriately low endogenous erythropoietin levels. While taking AZT, their erythropoietin levels usually increase but still remain disproportionately depressed.[69] Given the success of rHuEPO in treating anemia in other settings of erythropoietin deficiency, a randomized, placebo-controlled study was undertaken involving 63 anemic AIDS patients receiving AZT therapy.[79] Of these 63 patients, 48 (79%) had baseline
erythropoietin levels less than 500 IU/L and 13 (21%) had levels greater than 500 IU/L. Patients who received rHuEPO (100 units/kg subcutaneously three times per week) and had endogenous erythropoietin levels less than 500 IU/L required few blood transfusions. In contrast, those with erythropoietin levels greater than 500 IU/L required just as many transfusions as did placebo-treated controls.

These findings were subsequently united with those of three additional placebo-controlled studies in a meta-analysis seeking to clarify the effects of rHuEPO in HIV-associated anemia. Once again, only when erythropoietin levels were less than 500 IU/L did patients benefit from hormone injections.[70] These benefits were reflected by decreased transfusion requirements, improved hemoglobin levels, and an increased sense of well-being. Moreover, rHuEPO did not potentiate HIV infection (as indicated by in vitro assays of HIV proliferation, serum p24 antigen levels, and total lymphocyte counts) or increase the risk of opportunistic infections.

Drug side effects were negligible in these cohorts. In other settings, such as end-stage renal disease or myeloma, non-HIV-infected patients may rarely develop hypertension, embolic phenomena, rash, seizures, and pyrexia, or may complain of headaches and fatigue.

Although less well studied, it appears that rHuEPO is also beneficial in ameliorating anemia in those with HIV infection and end-stage renal disease, with and without diabetes.[80] In addition, in a large open-label study[81] and a smaller randomized study,[82] anemic AIDS patients treated with hematopoietic hormone, but not AZT, required significantly fewer blood transfusions. Responses correlated best with low baseline erythropoietin levels.

Erythropoietin therapy is more effective when given subcutaneously than intravenously.[83] The longer half-life of subcutaneous injections produces a lower but more sustained serum erythropoietin level. Myeloid-CSF may also modulate the effects of rHuEPO. For example, Miles and colleagues have shown that, in the absence of erythropoietin treatment, G-CSF may also increase red blood cell production and the number of circulating BFU-E.[84] Using rHuEPO and G-CSF together may offer synergistic benefits when treating anemic patients.[85]

Cost vs Benefit

Although rigorous cost-benefit analyses of rHuEPO have not been applied to HIV-associated anemia, the average cost to maintain a patient on this drug at a standard dose of 150 units/kg three times weekly for 4 months is approximately $5,000, assuming that the patient self-administers the medication.[83] The average cost for a 2-unit packed red blood cell transfusion is approximately $250, and rises to more than $700 if nursing time and other resources are considered. For patients who require less than 4 to 6 units of transfused blood per month, rHuEPO becomes a very expensive option.

Are the costs of this drug fully offset by the savings it achieves in decreasing the need for transfusions and the treatment of transfusion-related toxicities? This is debatable, particularly in the setting of anemia induced by AZT, ganciclovir, trimethoprim-sulfamethoxazole, or other drugs, for which alternative therapies exist. It is also debatable whether the documented improvements in quality of life associated with rHuEPO therapy justify the increased expenditures associated with its use.

Additional clinical studies aimed at improving the cost-benefit of rHuEPO are needed.[86] In the meantime, several authors have offered practical recommendations when evaluating anemic patients for rHuEPO therapy (Table 4).[17,83,87,88]

Neutropenia and Infection in Patients With AIDS

Although the link between the degree and length of neutropenia and risk of infections is well documented in cancer patients,[89] this association is less well established in HIV patients.[90-93] Despite the fact that neutropenia occurs in approximately 17% of symptomatic patients with HIV, as immunodeficiency worsens, the frequency of bacterial infections increases.[94] Several recent retrospective studies have attempted to better quantify the relationship between neutropenia and bacteremia in AIDS patients[95-97] and to assess the impact of this association on morbidity and mortality.[97]

In one such analysis, Keiser and associates conducted a case-control study comparing AIDS patients with ANC levels less than 1,000 cells/mm$^3$ with controls matched for CD4+ cell counts, sex, and age.[95] Multivariate analysis indicated that neutropenia (relative risk, 14.9; P = .026) and the presence of central venous catheters (relative risk, 3.8; P = .03) posed the greatest risks for bacteremia. How long and to what extent patients remain neutropenic are additional variables that affect their risk of bacterial infection. In a matched cohort study, Moore and colleagues compared the incidence of bacterial infections in 118 neutropenic AIDS patients (ANC less than 1,000 cells/mm$^3$) and 118
nonneutropenic controls matched for CD4+ lymphocyte count, use of intravenous drugs, and length of follow-up.[96] The relative risk of bacterial infections was 2.33 for patients with an ANC less than 1,000 cells/mm$^3$ and 7.92 for those with an ANC less than 500 cells/mm$^3$. The number of severe bacterial infections was also highest among those with the lowest ANCs.

Most recently, Jacobson and colleagues collected data from San Francisco General Hospital’s HIV clinic-based population of more than 2,000 individuals between 1992 and 1993.[97] Focusing their investigation on the severity of neutropenia and risk of significant bacterial infections in patients with HIV disease (based on the number and length of hospitalizations for bacterial infections), they found a continuous, exponential, inverse relationship between the incidence of hospitalization for bacterial infections and ANC stratum (with approximately twofold increases in incidence as ANC values decreased categorically from 750-1,000 cells/mm$^3$ to 300-499 cells/mm$^3$ to less than 300 cells/mm$^3$). Although absolute CD4+ cell count, age, gender, and race were taken into account, only the severity and duration of neutropenia and black race were significant predictors of the need for in-hospital treatment of bacterial infections.

Inherent in each of these retrospective analyses are difficulties in controlling a myriad of variables, including delay in diagnosis of infection, use of inpatient and outpatient antibiotic therapies, institutional resources, and patients’ ability to access medical care. Nonetheless, these studies emphasize that clinicians need to be aware of the enhanced risk of neutropenic bacteremia in patients infected with HIV. This subset is the target for prospective studies designed to prevent neutropenia and infection.

**Use of Neutrophil Growth Factors in AIDS**

Groopman and colleagues were the first to conduct a clinical study of the dose-related effects of administering myeloid growth factors to AIDS patients. They treated 16 patients with total leukocyte counts of ≤ 3,000 cells/mm$^3$ with GM-CSF by continuous infusion at doses ranging from 0.5 to 8 µg/kg/d.[98] Granulocyte counts increased rapidly but, the responses were not durable and within 48 hours of stopping growth factor support, white blood cell counts had returned to basal levels. Reversible toxicities included fever, facial flushing, transient skin rash, transaminase elevation, and local vein irritation.

Subsequently, two phase III studies evaluated GM-CSF in conjunction with ganciclovir for CMV retinitis[99] or following cytotoxic chemotherapy (cyclophosphamide, doxorubicin, Oncovin, and prednisone [CHOP]) for AIDS-related NHL.[100] In the CMV trial, 51 patients were randomized to receive intravenous ganciclovir with or without growth factor support. Those treated with GM-CSF experienced fewer days with an ANC less than 750 cells/mm$^3$ (P = .05). Although a trend toward maintenance of ganciclovir dosing and a reduction in the incidence of ocular relapses was noted, this did not achieve statistical significance, owing perhaps to the small number of accrued patients. In the lymphoma trial, patients who received GM-CSF experienced fewer neutropenic episodes and were hospitalized less frequently, but growth factor support did not have an impact on their survival or rate of relapse.

Although studies seeking to define the impact of growth factors on maintaining dose intensity in AIDS-related NHL are ongoing,[101] the importance of such a strategy is controversial.[102] ACTG study 142 showed that a less intensive chemotherapy strategy consisting of the combination of methotrexate, bleomycin, Adriamycin, cyclophosphamide, Oncovin, and dexamethasone (m-BACOD) could achieve results comparable to those of more myelosuppressive chemotherapy with concomitant growth factor support.[103]

The efficacy of G-CSF in patients with neutropenia and HIV infection has also been explored, originally in a small phase I/II trial of 11 subjects with neutropenia and AIDS or symptomatic HIV infection.[104] In that trial, all patients responded to G-CSF (100 to 200 µg/m$^2$/d) with significantly increased neutrophil counts. In other clinical settings where neutropenia is common, patients taking AZT or ganciclovir have achieved similar granulocyte count elevations.[105-108] A large phase III trial of HIV-positive individuals with ANCs between 500 and 750 cells/mm$^3$ is expected to provide further information on the impact of this growth factor on clinical outcomes.

Although responses to intravenous growth factors are transient, numerous studies indicate that long-term subcutaneous therapy with G-CSF and GM-CSF can produce sustained increases in granulocyte counts without depleting marrow stem-cell activity.[104,106,107,109,110] GM-CSF, however, is more likely to lead to dose-limiting side effects, especially fever, myalgias, and general malaise.[110] The broader range of action of GM-CSF as compared with G-CSF may partly explain this worse clinical tolerance.[111]
Side effects are seen at low doses (1 to 2.5 µg/kg/d) of GM-CSF and become more pronounced when it is used for more than a few months. For example, more than 60% of patients who received GM-CSF in the CHOP-AIDS lymphoma study had at least one of these symptoms, compared with CHOP-treated control patients who did not receive GM-CSF.[100] Similarly, in a trial of AZT, interferon-alfa, and GM-CSF, fatigue and asthenia limited long-term tolerance of GM-CSF.[112] This is one reason why many clinicians use G-CSF instead of GM-CSF in neutropenic AIDS patients.

**Effects of G-CSF and GM-CSF on HIV Replication**

Several in vitro studies indicate that GM-CSF, M-CSF, IL-6, and IL-3, but not G-CSF, may augment HIV replication.[113,114] Other investigators have noted opposite results, leading them to conclude that variations in experimental conditions, rather than a true biological difference, may determine which outcome is seen.[115]

In vitro, GM-CSF has also been shown to markedly augment the antiretroviral effect of AZT, apparently by increasing intracellular levels of the biologically active triphosphate form.[116] This effect is not generalizable to all nucleoside analog reverse transcriptase inhibitors; both ddl and ddC failed to prevent GM-CSF-induced increases in viral replication, whereas D4T appeared to be effective in a manner similar to that of AZT.

The clinical data regarding this issue generally antedate the availability of sensitive measures of circulating virus, and their results are conflicting. Kaplan and colleagues found that when patients received GM-CSF with each cycle of CHOP chemotherapy, HIV-p24 antigen levels rose.[100] Pluda and associates observed the same effect when they gave GM-CSF on alternating weeks to AIDS patients already receiving AZT.[109]

In contrast, when GM-CSF was added to the regimen of interferon-alfa and AZT for AIDS-related Kaposi's sarcoma, no increase in serum p24 antigen level was detected.[117] Furthermore, in the GM-CSF/ganciclovir trial,[99] and the original GM-CSF trial for neutropenic AIDS patients,[98] no detectable difference in p24 antigen levels was seen among those who received GM-CSF. In the randomized trial of G-CSF and erythropoietin,[84] and, most recently, in a GM-CSF-AIDS lymphoma trial (involving infusional chemotherapy and concomitant antiretroviral therapy),[101] no significant increase in measures of HIV viral replications was seen.

In an effort to clarify this issue, patients receiving a stable AZT dosage were evaluated at baseline, during daily administration of GM-CSF at one of three dose levels (50, 125, or 250 mg/m²/d) for 4 weeks, and during a 4-week GM-CSF wash-out period.[118] No consistent changes were seen in any of the four parameters of virus activity measured, despite evidence of GM-CSF activity and a trend toward increased intracellular AZT levels.

**Conclusions and Perspectives**

Based on recent findings amply demonstrating an increased risk of serious bacterial infections among HIV-infected patients with ANCs less than 1,000 cells/mm³,[93-97] some form of intervention appears to be warranted when neutropenia is caused by myelosuppressive agents, such as ganciclovir, trimethoprim-sulfamethoxazole, and AZT. Switching the patient to a nonhemotoxic alternative or continuing myelosuppressive therapy with concomitant growth factor support are options that can be used to reduce morbidity and mortality associated with serious bacterial infections.[97,119]

Nonetheless, because of the retrospective nature of the studies described, and the difficulty in controlling for a variety of important clinical factors, assumptions regarding the efficacy of these strategies should be viewed cautiously. Prospective studies controlling for such variables as the presence of central venous catheters, intravenous drug use, and the use of prophylactic antimicrobial agents are in progress and should shed additional light on the appropriate use of CSFs.

Clinical end points that need to be considered include improvements in patient compliance with therapy, reduction in days of hospitalization and infection rates, and improvement in overall survival. Given the high cost of growth factor therapy, an exploration of alternative factor dosing regimens in AIDS is also essential.[120] Clinicians experienced in treating cytopenic AIDS patients often use alternate-day or twice-weekly schedules. Capturing and correlating this information with clinical end points of effectiveness are crucial with regard to the economics of AIDS care and patient acceptance. Cost analyses need to be performed. At least one study showed minimal benefit but a 77% increase in cost when growth factor therapy was chosen over alternative drug selection.[86] Pending the results of such analyses, Table 5 offers practical recommendations when one is considering myeloid-CSF therapy for HIV-infected individuals.

**Alternative Uses of Growth Factors**
The use of growth factors to minimize HIV-associated cytopenias has been the focus of most clinical trials. However, several alternative uses may be envisioned, some of which are being tested currently. For example, some AIDS patients show defects in neutrophil and macrophage function.[121]

In the original GM-CSF study by Groopman et al, two such patients were identified.[98] In both, defects in intracellular killing were corrected during GM-CSF administration. Improvement in neutrophil function was likewise seen in a G-CSF study.[85]

The potential benefits of GM-CSF in augmenting macrophage function have led to other clinical trials of GM-CSF in MAI-related sepsis, cryptococcal meningitis, and recalcitrant Candida infections.[3] In one preliminary study of GM-CSF in patients with cryptococcal meningitis, growth factor given in conjunction with amphotericin B cleared C neoformans cultured from spinal fluid faster than amphotericin B alone.[122] Use of growth factors to augment function of these cells may prove useful in AIDS, particularly in patients with fungal or mycobacterial disease who no longer respond to conventional drug therapy.

**Newer Cytokines**

As our understanding of the complex pathogenesis of HIV-associated disease unfolds, so too will our understanding of the intricate cytokine network that affects hematopoiesis. Recent in vitro and in vivo studies looking at the benefits of the newer growth factors and interleukins are generating great excitement in the field of retroviral research.[123-126] These agents, used in conjunction with other novel strategies, such as anti-HIV-gene therapy,[127] promise not only to reduce the bone marrow suppression associated with HIV and its treatment but also to reconstitute the host immune system and, ultimately, change the natural history of this devastating illness.

**References:**


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