Anemia in the Setting of Cancer and Human Immunodeficiency Virus

Alexandra M. Levine
Division of Hematology, Keck School of Medicine, University of Southern California, Los Angeles, California

Anemia commonly occurs in patients with cancer or human immunodeficiency virus (HIV) infection as a result of the disease, its treatment, or both. The negative impact of anemia on patient quality of life (QOL), functional status, and treatment outcomes underscores the need for its correction in these patients. In anemic patients with cancer or HIV infection, treatment with epoetin alfa increases hemoglobin (Hb) levels, decreases transfusion requirements, and improves QOL. In both settings, the gains in overall QOL have been significantly and directly related to increases in Hb, with maximum QOL gains in the range of Hb levels of 11–13 g/dL, supporting the need to achieve and maintain Hb levels $\geq 12$ g/dL in an effort to preserve and maximize QOL benefits. A potential survival benefit has also been associated with correction of anemia in patients with HIV infection—and possibly in those with cancer as well.

IMPACT OF ANEMIA IN CANCER AND HIV

Anemia is a common hematologic abnormality in patients with cancer or HIV infection, resulting from the disease or its treatment, and it may increase in frequency and/or severity with advancing disease [1–4]. Anemia can result in a wide range of symptoms and impairments in almost every organ and tissue [5], with a potentially profound adverse impact on patients’ quality of life (QOL) and ability to perform physical activities involved with daily living [1, 6–9]. Recent data suggest that anemia is an independent predictor of survival in patients with HIV infection, where it has been associated with increased risk of HIV disease progression and decreased survival [10–14]. In addition, studies suggest that correction of anemia in HIV-infected patients is associated with improved survival [11, 12]. A relationship between anemia and decreased survival in patients with cancer has also been suggested [15, 16]. In the context of these findings, the negative impact of anemia on patient well-being and on treatment outcome and survival underscores the need for corrective treatment in these patient populations.

The etiology of anemia in the settings of cancer or HIV is complex and often multifactorial [4, 17, 18]. Potential causes of anemia in the cancer population include chemotherapy- or radiotherapy-induced myelosuppression; blood loss; hemolysis; tumor involvement of the marrow; and deficiencies in iron or folic acid [1, 18]. Potential causes of anemia in HIV-infected patients also include deficiencies of iron, folic acid, and vitamin B$_{12}$, as well as HIV disease itself; opportunistic infections (e.g., cytomegalovirus, parvovirus B19, mycobacterial disease); infiltrative disease of the bone marrow; and the use of multiple medications, including antiretroviral agents, especially zidovudine [4, 19]. Further, the anemia of chronic disease is common in both disorders and is typically a normochromic, normocytic anemia with normal or increased iron stores that occurs in association with inflammatory or infectious diseases [20]. In the anemia of chronic disease due to cancer or HIV infection, erythropoietin synthesis is impaired,
and the erythropoietin response to anemia is blunted, with levels that are inappropriately low for the degree of anemia compared with levels present in iron-deficiency anemia [21–25]. The pathogenesis of anemia of chronic disease appears to involve increased release of inflammatory cytokines such as IL-1 and IFN-γ, resulting in suppression of erythropoietin receptor expression, inhibition of the production of erythroid precursors in the bone marrow, and impairment of iron use [18, 26, 27]. The blunted endogenous erythropoietin response associated with the anemia of chronic disease underlies the need for higher exogenous doses of recombinant human erythropoietin (epoetin alfa) necessary in the treatment of anemia associated with cancer or HIV infection compared with the doses necessary in chronic kidney disease [28].

In adult patients with nonmyeloid malignancies who receive cytotoxic chemotherapy, mild to moderate anemia (hemoglobin [Hb] 9.5–10.9 g/dL and 8.0–9.4 g/dL, respectively, as defined by the World Health Organization) occurs in ∼50%–75% of patients [17]. In terms of HIV infection, historically, anemia was common, occurring in >50%–75% of patients in the pre-HAART era, depending on immune status and HIV viral load. High-dose zidovudine contributed to anemia as well. With the introduction of HAART and the use of lower zidovudine doses in current treatment regimens, the prevalence and severity of anemia in the HIV-infected population has declined, but it remains a clinically relevant issue [29]. Recent data suggest that mild to moderate anemia remains common in the HAART era [13, 30, 31], even though Hb levels may increase or return to normal values in some patients who are anemic at the start of HAART [13, 31]. For example, in a subset analysis of data from the EuroSIDA study, a large prospective, observational study including >7300 nonselected HIV-positive patients, anemia resolved after 12 months in ∼30% of patients who presented with anemia at initiation of HAART, but mild to moderate anemia remained in 46% of patients [13]. In patients who are not anemic at the initiation of therapy, HAART may also decrease the risk of developing anemia over time [32].

Clinical symptoms of anemia may include dyspnea on exertion, weakness, increased heart rate, dizziness, headache, chest pain, and/or cognitive impairments [5, 17]. Fatigue is a major component of the symptomatology of anemia and occurs in most patients with cancer [6, 7, 33]. Fatigue is typically perceived by patients with cancer to be a greater problem than pain [6, 7, 34] and is the symptom with the greatest apparent adverse impact on QOL [6, 7]. In this patient population, fatigue may also be an independent predictor of loss of function [35]. Similarly, fatigue is common among HIV-infected patients, with a corresponding adverse impact on QOL and functional abilities [8, 9, 29, 36].

### QOL ASSESSMENT IN PATIENTS WITH CANCER

Health-related QOL is an important consideration in patients with cancer or HIV infection. As treatments for these diseases improve, patients live longer and wish to maintain or improve QOL. Consequently, many current clinical trials are assessing not only the efficacy and safety of various treatments, but also treatment-related changes in QOL parameters. Instruments used to assess QOL may address specific diseases and/or symptoms or overall well-being of patients. It is important that the instrument used be both validated and reliable so that the results may be analyzed and interpreted appropriately. Whether QOL measures are used in clinical trials or in the clinical setting, it is also important that they be simple, relevant, and easily recorded by the patient or health care provider [37]. Various instruments have been used to assess QOL in the cancer setting, including the Functional Assessment of Cancer Therapy—General (FACT-G) [38], the Functional Assessment of Cancer Therapy—Anemia (FACT-An) [39, 40], and the Linear Analog Scale Assessment (LASA) [37]. FACT-G (version 2) is a 28-item questionnaire that evaluates the domains of physical, social/family, and functional well-being; relationship with the physician; and emotional well-being [38]. FACT-G is a

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<th>Table 1. Epoetin alfa community-based studies of cancer-related anemia.</th>
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<td>(N = 2342)</td>
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<td>Open label, nonrandomized</td>
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<td>Anemic</td>
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<td>Initial epoetin alfa dose: 150 U/kg sc t.i.w.; increase to 300 U/kg sc t.i.w. if inadequate response at 8 wk</td>
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<td><strong>Demetri study [45]</strong>&lt;sup&gt;**&lt;/sup&gt;</td>
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**NOTE.**  Hb, hemoglobin; sc, subcutaneous; t.i.w., 3 times weekly; q.w., weekly.
validated scale that was designed specifically for patients with cancer but has also been used as a core component in other instruments to evaluate QOL in patients with other diseases, including HIV (i.e., the Functional Assessment of Human Immunodeficiency Virus Infection [FAHI] instrument) [41, 42]. Another instrument used to assess QOL in anemic patients with cancer is the FACT-An, which is a validated scale consisting of 28 items of the FACT-G plus 13 items related to fatigue (the Fatigue Subscale) and 7 items addressing other concerns related to anemia but unrelated to fatigue [39, 40].

With LASA, the patient self-reports his or her well-being by the use of three 100-mm linear subscales: energy level, ability to perform daily activities, and overall QOL. For example, in assessing the activities of daily living, the patient is asked, “How would you rate your ability to do daily activities during the past week?” and the patient is instructed to place a mark on a 100-mm line, with 0 representing “as low as could be” and 100 representing “as high as could be” [43]. The scale was developed specifically for patients with cancer but also has been used to evaluate QOL in patients with other chronic diseases, including HIV infection [44]. LASA is a simple and rapidly completed assessment that has demonstrated validity and reliability [37]; further, it can detect small changes in patient perceptions [45].

**USE OF EPOETIN ALFA IN PATIENTS WITH CANCER**

Randomized, placebo-controlled clinical studies have demonstrated the effectiveness and safety of epoetin alfa (PROCRIT; Ortho Biotech Products), which is biologically and immunologically indistinguishable from endogenous erythropoietin, for the treatment of anemia in patients with nonmyeloid malignancies who are receiving concomitant chemotherapy [46–49]. Epoetin alfa is also effective in the treatment of cancer-related anemia in patients not receiving chemotherapy [46, 50, 51]. Improvements in QOL and functional status associated with epoetin alfa–induced increases in Hb have been reported in a number of studies in anemic cancer patients receiving chemotherapy [46, 47, 49, 50, 52].

Three recent, large, open-label, nonrandomized, multicenter, community-based clinical studies enrolling >7500 anemic patients with cancer have shown that epoetin alfa therapy increases Hb levels and improves QOL and functional status of treated patients (table 1) [43, 45, 53]. All patients in these studies had solid or nonmyeloid malignancies and were receiving concomitant chemotherapy [43, 45, 53]. In the first study, the initial dose of epoetin alfa was 150 U/kg sc t.i.w.; if the hematologic response was not adequate after 8 weeks, the dose of epoetin alfa could be increased to 300 U/kg t.i.w. [43]. Treatment with epoetin alfa was continued for up to 4 months. Patients self-rated their energy level, ability to perform daily activities, and overall QOL by LASA [43]. Of 2342 patients enrolled, data were available for 2030 patients, of whom 1047 completed the study [43]. A significant increase in Hb was observed from baseline to each monthly visit, with a mean increase of 1.8 g/dL for patients with both a baseline and a final measurement available (P < .001) [43]. Epoetin alfa therapy was also associated with a significant decrease in the proportion of patients requiring transfusions (baseline to final value, P < .001) [43]. Thus, before the institution of epoetin alfa, 21.9% of patients required transfusions, with a mean transfusion requirement of 0.57 U per patient per month. At month 2 of therapy, 14.8% of patients required transfusion, with a mean requirement of 0.40 U per patient per month. At month 4 of epoetin alfa therapy, 10.3% of patients required transfusions, with a mean requirement of 0.29 U per patient per month. Mean LASA scores for energy, activity, and overall QOL were significantly higher at completion of epoetin alfa therapy compared with baseline (P < .001 for each subscale) [43]. These improvements in QOL scores correlated (energy: r = .30, activity: r = .28, overall QOL: r = .27) with the magnitude of the Hb increase from baseline [43]. In a retrospective analysis of a subset of 759 patients, the QOL improvements were found to be correlated with increases in Hb level, and importantly, they were independent of tumor response [43].

A subsequent study enrolling 2370 patients was undertaken to further assess the effects of epoetin alfa on functional outcomes and QOL and to prospectively evaluate the impact of tumor response [45]. QOL was assessed by FACT-An and LASA [45]. Patients initially received epoetin alfa at a dosage of 10,000 U sc t.i.w. [45]. If the Hb increase was <1.0 g/dL after 4 weeks of therapy, epoetin alfa dosage was increased to 20,000 U t.i.w. [45]. Epoetin alfa therapy was continued for a maximum of 16 weeks in patients who showed evidence of a hematologic response (increase in Hb level of ≥1.0 g/dL after the initial 4 weeks of therapy or after an additional 4 weeks of therapy at the increased dosage) [45]. A mean Hb increase of 2.0 g/dL (P < .001) was observed among 2237 patients [45]. Maximum Hb levels were achieved between 3 and 4 months after initiation of epoetin alfa treatment for all patients across all tumor types [45]. The percentage of patients requiring blood transfusions significantly decreased (P < .001) after 2 months, and this improvement was maintained over the course of the study [45]. FACT-An scores significantly (P < .001) improved from baseline to final evaluation [45]. Mean LASA scores at the completion of epoetin alfa therapy for energy level, activity level, and overall well-being were also significantly improved from baseline (P < .001 for each subscale) [45]. Improvements in QOL were significantly correlated with increasing Hb levels and were confirmed to be independent of tumor response [45]. Patients...
achieving a mean Hb level increase ≥2 g/dL reported the greatest improvements in FACT-An total and anemia subscale scores [45]. Patients who achieved an Hb level increase of 0 to <2 g/dL or ≥2 g/dL had significant improvements in the FACT-An anemia subscale score independent of whether the tumor response to chemotherapy was complete, partial, or stable (figure 1) [45]. As measured by LASA, patients who achieved a complete response, partial response, or stable disease without an increase in Hb level did not have a meaningful or significant increase in QOL [45]. Although patients experiencing progressive disease showed an overall decline in QOL over the course of the study, patients with progressive disease who had an Hb increase ≥2 g/dL experienced a relatively stable QOL compared with patients with little or no increase in Hb levels [45].

A third study that enrolled 3012 patients was similar to the others, with the exception that epoetin alfa was administered once per week, as opposed to thrice weekly. With this more convenient dosing schedule, effects on hematologic status, functional outcomes, and QOL were assessed [53]. Patients initially received epoetin alfa 40,000 U sc q.w. with dose escalation to 60,000 U q.w. if Hb did not increase by at least 1.0 g/dL after 4 weeks of therapy [53]. Patients were treated for a maximum of 16 weeks [53]. The mean Hb increase from baseline to final assessment among 2869 assessable patients with at least 2 Hb measurements was 1.8 ± 1.8 g/dL (P < .001), and the mean final Hb level was 11.3 ± 1.8 g/dL [53]. The mean Hb increase and final Hb level were similar to those observed with thrice-weekly dosing of epoetin alfa (figure 2) [43, 45]. The percentage of patients who required transfusion and the number of units transfused per patient decreased significantly (P < .007) by month 2 and continued to decrease during the course of the study [53]. The mean percentage change in LASA scores in energy level, ability to perform daily activities, and overall QOL stratified by Hb change from baseline are depicted in figure 3 [53]. As shown, the improvements in LASA scores with q.w. epoetin alfa dosing were similar to the LASA improvements observed in the studies evaluating thrice-weekly dosing of epoetin alfa [43, 45]. The safety profile of weekly epoetin alfa administration was also similar to the safety profile observed with thrice-weekly dosing [43, 45, 53].

In an incremental analysis of clinical and outcomes data from the combined results of the first 2 community-based studies (n = 4382) [43, 45], a statistically significant (P < .01) relationship between Hb and QOL was identified [54]. Increases in Hb as a result of epoetin alfa therapy were associated with QOL improvements across the Hb range of 8–14 g/dL. In a longitudinal analysis of data from the second community-based study [45], the largest improvement in overall QOL for each

![Figure 1](image.png)

**Figure 1.** Quality of life (FACT-An Anemia subscale) analyzed by tumor response and Hb level changes from baseline to final assessment in anemic cancer patients treated with epoetin alfa (n = 1484) [45]. Adapted with permission from Demetri GD, Kris M, Wade J, Degos L, Cella D, for the Procrit Study Group. Quality-of-life benefit in chemotherapy patients treated with epoetin alfa is independent of disease response or tumor type: results from a prospective community oncology study. J Clin Oncol 1998; 16: 3412–25 [45]. *Significantly different from baseline (P < .05). †Significantly different from baseline (P < .01). ‡Significantly different from previous Hb group (P < .05). §Significantly different from previous Hb group (P < .01). FACT-An, Functional Assessment of Cancer Therapy-Anemia; Hb, hemoglobin.
Figure 2. Increases in Hb level from baseline in epoetin alfa community-based studies in patients with anemia and nonmyeloid malignancies who were receiving chemotherapy [43, 45, 53]. *Significantly different from baseline (P < .001). Hb, hemoglobin; TIW, 3 times weekly; QW, once weekly.

1-g/dL change in Hb occurred when the Hb level increased from 11 to 12 g/dL (range, 11–13 g/dL) (figure 4). Similar findings have been reported in anemic HIV-infected patients treated with epoetin alfa [55]. These data support maintaining an Hb level $\geq$12 g/dL in chemotherapy patients to preserve QOL.

Recent data suggest that epoetin alfa may also have an effect on survival in anemic cancer patients receiving chemotherapy. In a double-blind trial, anemic patients receiving nonplatinum chemotherapy for solid or nonmyeloid hematologic malignancies were randomized to receive either epoetin alfa (150–300

Figure 3. Percentage change in LASA scores by Hb level change from baseline in anemic cancer patients treated with weekly doses of epoetin alfa [53]. *Significantly different from baseline to final assessment (P < .01). †Significantly different from previous Hb group (P < .01). LASA, Linear Analog Scale Assessment; Hb, hemoglobin; QOL, quality of life. Adapted with permission from Gabrilove JL, Cleeland CS, Livingston RB, Sarokhan B, Winer E, Einhorn LH. Clinical evaluation of once-weekly dosing of epoetin alfa in chemotherapy patients: improvements in hemoglobin and quality of life similar to three-times-weekly dosing. J Clin Oncol 2001; 19:2875–82 [53].
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U/kg \[n = 251\] administered sc t.i.w.) or placebo \(n = 124\) for 12–24 weeks \[16\]. Compared with placebo, epoetin alfa significantly decreased transfusion requirements \((P = .0057)\) and increased Hb levels \((P < .001)\) \[16\]. Improvements in QOL domains, including energy level, ability to perform daily activities, and fatigue, as measured by FACT-An and LASA, were significantly greater in patients receiving epoetin alfa versus placebo \((P ≤ .0048)\) \[16\]. Increases in Hb levels were significantly and strongly correlated with QOL improvements \((P ≤ .0325)\) \[16\]. Although the study was not designed or powered for survival as an end point, the study protocol was amended before unblinding and study termination to permit prospective analysis of survival \[16\]. Survival was assessed 12 months after the last enrolled patient completed the study (median follow-up, 26 months) \[16\]. The median survival time for patients receiving epoetin alfa was 17 months versus 11 months for patients receiving placebo \[16\]. The Kaplan-Meier 12-month estimate of survival was 60% for the epoetin alfa group and 49% for the placebo group \[16\]. Although these differences were not statistically significant, the trend in overall survival favored use of epoetin alfa \((P = .13, \text{log-rank test})\) \[16\]. A similar pattern favoring the epoetin alfa group was observed in patients with solid tumors or hematologic malignancies when analyzed by tumor stratum. As expected, patients with hematologic malignancies in both treatment arms had a lower mortality rate \[16\]. By use of the Cox regression model, the risk of dying during the entire follow-up period was \(~31\%\) lower for epoetin alfa-treated patients compared with placebo-treated patients (estimated hazards ratio, 1.309; \(P = .052)\) \[16\].

It should be noted that variables that influence survival, such as disease stage, bone marrow involvement, chemotherapy intensity, and disease progression, were not controlled for or stratified in the study or collected during the follow-up period; hence, these results must be interpreted with caution. Further evaluation of a potential survival benefit is warranted.

QOL ASSESSMENT IN PATIENTS WITH HIV INFECTION

Commonly used QOL instruments in patients with HIV infection include the Medical Outcomes Study—HIV (MOS-HIV) Health Survey, the MOS Short Form-36 (SF-36), LASA, and FAHI. The MOS-HIV is a brief disease-specific health status measure that has been used extensively in clinical trials of HIV-
Figure 5. Mean Hb (A) and overall QOL changes assessed by LASA (B) in patients with anemia and HIV infection who were treated with weekly (QW) and thrice-weekly (TIW) dosing regimens of epoetin alfa [63]. Adapted with permission from Grossman H, Bowers P, Leitz G, for the 010 Study Group. Once-weekly dosing of 40,000 epoetin alfa is as effective as thrice-weekly dosing among anemic HIV+ patients [abstract I-254] In: Proceedings of the 41st Interscience Conference on Antimicrobial Agents and Chemotherapy (Chicago, IL), 2001: 322–3. Hb, hemoglobin; QOL, quality of life; LASA, Linear Analog Scale Assessment.

infected patients [56]. The questionnaire consists of 35 items covering 10 dimensions, including general health perceptions, pain, physical functioning, role functioning, social functioning, mental health, cognitive functioning, energy/fatigue, health distress, and QOL [56]. The subscales are scored on a 0–100 scale, with higher scores indicating better health [56]. Physical and mental health summary scores also can be generated [56]. The MOS-HIV multi-item scales have shown internal consistency, responsiveness to improving or worsening disease, and good construct validity [56].

The MOS SF-36 was constructed to expand the measurement of health concepts and improve precision over the SF-20 [57]. SF-36 is a 36-item questionnaire consisting of 8 health concepts, including physical functioning, emotions, mental health, role
functioning, bodily pain, social functioning, general health perceptions, and vitality [57]. The survey was designed to measure a variety of health states, including well-being and personal evaluations of health [57].

**USE OF EPOETIN ALFA IN PATIENTS WITH HIV INFECTION**

Epoetin alfa was evaluated more than a decade ago as a potential therapy for anemia in HIV-infected patients receiving zidovudine because of the drug’s propensity to cause anemia. Furthermore, with the expanding HIV-AIDS epidemic and the anticipated increase in transfusion requirements in this patient population, with its attendant risks (including transmission of other blood-borne infections, and fluid or iron overload), several trials of epoetin alfa were initiated [58]. At that time, it had also been observed that endogenous erythropoietin levels in patients with HIV-AIDS were usually inappropriately low for the degree of anemia [23]. The efficacy of epoetin alfa in this setting was demonstrated by four 12-week, randomized, double-blind, placebo-controlled, multicenter clinical studies enrolling 297 anemic (hematocrit <30%) patients with AIDS who were receiving zidovudine therapy [44]. Patients received either epoetin alfa (100–200 U/kg) or placebo by iv or sc administration t.i.w. for 12 weeks [44]. Among patients with low erythropoietin levels (≤500 IU/L), epoetin alfa significantly decreased the mean number of units of blood transfused per patient during the 12-week study period, compared with placebo (3.2 U and 5.3 U, respectively; P = .003) and increased the mean hematocrit from baseline (4.6 percentage points and 0.5 percentage points, respectively; P < .001) [44].

In patients achieving a hematocrit of at least 38% with epoetin alfa therapy, significant improvements were observed in QOL parameters on the basis of LASA [44]. Similar improvements in QOL were reported with epoetin alfa therapy in a subgroup of anemic patients with AIDS (n = 251) [59] participating in an open-label, multicenter epoetin alfa investigational new drug protocol (N = 1943) [60]. In that subgroup analysis, patients whose hematocrit increased to ≥38% had significantly (P < .05) better physical well-being and functioning, as well as improvements in energy, health perception, home management, and role function, than did patients whose anemia was not corrected [59]. Other data also indicate that epoetin alfa is effective in treating anemic HIV-infected patients who are not receiving zidovudine [61]. Thus, in another subgroup analysis of 523 anemic patients with AIDS who were not receiving or had not received zidovudine, the increase in hematocrit and decrease in transfusion requirement were similar to those observed in anemic patients receiving zidovudine [61]. Many of these patients had anemia associated with chronic disease.

In a recent open-label, nonrandomized, community-based study of 221 anemic (Hb ≤11 g/dL) HIV-positive patients treated with epoetin alfa (100–300 U/kg sc t.i.w.), QOL was assessed by the FAHI [62]. Total QOL score and physical well-being subscale score improved significantly [62]. The greatest improvements in QOL and physical well-being were associated with increases in Hb level >2 g/dL, but even smaller increases in Hb had beneficial effects [62]. The improvements in QOL and physical well-being were significantly associated with changes in Hb level independent of changes in CD4+ cell counts, suggesting the improvements were due to epoetin alfa therapy and were not a function of improvements in underlying HIV disease [62]. The improvements in QOL and physical well-being were also independent of the baseline severity of anemia [62].

Recent studies of weekly administration of epoetin alfa have demonstrated the effectiveness of this dosing schedule in anemic HIV-infected patients [55, 63]. In a large, initial, open-label, multicenter study, anemic (Hb ≤11 g/dL) HIV-positive patients who were receiving stable antiretroviral therapy received epoetin alfa 40,000 U sc q.w. with titration to 60,000 U if Hb increased ≤1 g/dL at 4 weeks [55]. Epoetin alfa treatment was continued for 16 weeks. Study end points included changes in QOL as assessed by MOS-HIV Health Survey and LASA, changes in Hb, and changes in transfusion use [55]. In an efficacy analysis of 709 assessable patients, the mean Hb increase from baseline to final evaluation at week 16 was 2.7 ± 1.9 g/dL [55]. The mean Hb improvement from baseline was statistically significant (P < .05) at week 2 (1.3 g/dL), week 4 (2.1 g/dL), and week 8 (2.7 g/dL) and was maintained for the duration of the study [55]. No statistically significant differences in Hb improvement were noted across racial subgroups or in comparisons of patients who received zidovudine treatment and patients who did not receive zidovudine [55]. Hb improvements with epoetin alfa occurred independently of baseline CD4+ cell count and changes in CD4+ cell counts [55]. Transfusion requirements decreased significantly (P < .05) [55]. Mean improvements in LASA (41%) and MOS-HIV (37%) scores from baseline to final evaluation were statistically significant (P < .0001) [55], and corresponded to increases in Hb [55]. The maximum incremental increase in MOS-HIV Overall QOL occurred in the Hb range of 10–12 g/dL [55]. Similar to findings in patients with cancer [54], these results support maintaining an Hb level ≥12 g/dL in HIV-infected patients to maximize QOL benefits.

Preliminary results from a subsequent, randomized, prospective, open-label study by Grossman et al. [63] also demonstrate that weekly administration of epoetin alfa is as effective in increasing Hb levels and improving QOL as thrice-weekly administration in patients with HIV infection. Anemic (Hb <12 g/dL) HIV-positive patients receiving stable antiretroviral therapy were randomized to receive epoetin alfa doses of 100 U/
kg t.i.w. or 40,000 U q.w. for 16 weeks [63]. Study end points included changes in Hb and QOL as measured by LASA and MOS-HIV Health Survey [63]. An interim analysis included 174 patients (t.i.w. regimen, n = 83; q.w. regimen, n = 91) with no significant differences in baseline Hb, viral load, or CD4+ cell count [63]. A significant improvement in Hb and QOL was observed in both treatment groups at week 8 (P<.05) and was maintained until the end of the study [63]. At week 16 or at the final measurement, Hb and QOL were not significantly different between the weekly and thrice-weekly dosing arms (figure 5) [63]. The results of this study support the use of the more convenient weekly epoetin alfa administration regimen in HIV-infected patients with anemia.

CONSEQUENCES OF ANEMIA IN HIV INFECTION: DISEASE PROGRESSION AND MORTALITY

In an attempt to develop a prognostic scoring system for HIV-infected patients receiving HAART, Lundgren and colleagues [64] from the EuroSIDA Study evaluated 2027 patients who initiated HAART, from among an initial cohort of 8457 subjects. Data were then validated in 2 additional groups consisting of 1946 and 1442 patients, respectively. A total of 9.9% of patients experienced clinical progression (either a new AIDS-defining illness or death), representing an incidence of 3.9 per 100 person-years. Multivariate analysis revealed that 4 factors were independently associated with disease progression: most recent CD4+ count cell, HIV-1 viral load, clinical status at the initiation of HAART, and Hb level. Thus, with anemia defined as Hb of 8–14 g/dL for men and 8–12 g/dL for women, the relative hazard of disease progression or death was 2.2 (95% CI, 1.6–2.9, P<.0001), whereas for severe anemia (Hb <8 g/dL), the relative hazard was 7.1 (95% CI, 2.5–20.1, P = .0002).

Similarly, the Adult and Adolescent Spectrum of HIV Disease Surveillance Project found that anemia was associated with an increased risk of death, after controlling for other factors [12]. In patients with CD4+ cell counts of ≥200 cells/mm³, the presence of anemia was associated with a 148% greater risk of death than in nonanemic patients. In patients with CD4+ cell counts of <200 cells/mm³, anemia remained an independent risk factor for death, with a 56% greater likelihood of death than in nonanemic patients. Thus, even in patients with very low CD4+ cell counts, in whom opportunistic infections would constitute the major risk for death, anemia remained an independently significant indicator of poor prognosis. Note that the risk of death was 170% greater for those who failed to recover from anemia than for those in whom the anemia resolved [12].

The importance of treating anemia in HIV-infected patients was also shown by Moore and colleagues [10], who monitored 2348 HIV-infected patients during 1989–1996. Of these, 21% developed anemia (Hb level <9.4 g/dL). As in the study by Sullivan and colleagues [12], development of anemia was associated with shorter survival, when controlling for other prognostic factors. Notably, use of epoetin alfa was associated with a decreased risk of death (P = .002).

SUMMARY

Maintaining or improving overall QOL, the ability to perform daily activities, and functional status are important considerations for anemic patients with cancer or HIV infection, and Hb levels should be monitored. Treating anemia with epoetin alfa increases hematocrit and Hb levels, decreases transfusion requirements, and improves QOL and functional status in patients with cancer or HIV infection. Recent studies in both settings have demonstrated that gains in overall QOL are significantly and directly related to increases in Hbs, with maximum QOL gains in association with Hb levels in the range of 11–13 g/dL, underscoring the importance of achieving and maintaining near-normal Hb levels (≥12 g/dL) [16, 29]. Studies in both patient populations have shown that weekly administration of epoetin alfa produces Hb increases and QOL benefits similar to those obtained with thrice-weekly administration, which should increase patient convenience. Recent data raise the possibility of a potential survival benefit associated with correction of anemia in patients with cancer or HIV infection. Treating and correcting anemia with epoetin alfa in patients with cancer or HIV infection may have implications on morbidity and mortality in these populations.

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