CORRESPONDENCE

Relationship between Changes in Hemoglobin Level and Quality of Life during Chemotherapy in Anemic Cancer Patients Receiving Epoetin Alfa Therapy

Patients with cancer routinely experience moderate-to-severe anemia as a result of the hematopoietic blunting effects of either their malignancy or the subsequent therapy. Such anemia manifests itself primarily as a debilitating fatigue that leaves the patient unable to work or with a limited capacity to fulfill familial or social obligations; however, the potential consequences also include depression, vertigo, and nausea. The overall effect of these symptoms can be a significantly diminished quality of life (QOL).[1] It now is well established that treatment of anemia with erythropoietic agents increases hemoglobin (Hb) levels in a large proportion of patients and that this increase leads to an improved QOL.[2–5] What is less clear, however, is by how much or to what threshold level the Hb concentration must be raised to obtain these QOL benefits.

Crawford et al.[6] recently performed a retrospective analysis of two nonrandomized studies of anemic patients with cancer ($n = 4382$) who were receiving chemotherapy.[4,5] This retrospective analysis examined the correlation between incremental changes in Hb concentration and QOL as assessed by the 100-mm linear analog scale assessment. The authors demonstrated a direct correlation between Hb level and QOL ($P < 0.01$) and reported that the largest improvement in QOL resulting from a 1 g/dL change in Hb concentration occurred when Hb concentration increased from 11 to 12 g/dL. The authors concluded that the Hb level of anemic patients with cancer should be maintained at 11–13 g/dL to provide the greatest improvement in QOL. However, a recent study performed by our group found no support for the idea of a 'target' Hb level for improving each patient's QOL.[3] We conducted a randomized, placebo-controlled study of the effects of epoetin beta on Hb levels and QOL in severely anemic, transfusion-dependent patients with hematologic malignancies. QOL was assessed using the Functional Assessment of Cancer Therapy Anemia questionnaire. Although there was a statistically significant correlation ($P = 0.001$; $r = 0.32$) between final Hb concentration and changes in QOL score (Fig. 1), the data revealed considerable interindividual variability. For individual patients, an optimal Hb level for improvement of QOL could not be identified. More noteworthy is the finding that an increase of at least 2 g/dL from baseline (without transfusion) was significantly correlated with improvements in QOL in anemic patients with cancer. This finding is in general agreement with the work of Glimelius et al.,[7] who reported that patients who achieved increases in Hb concentration (as opposed to patients who reached a predefined target Hb level) experienced the most significant improvements in QOL.

In light of these data, it remains an open question as to

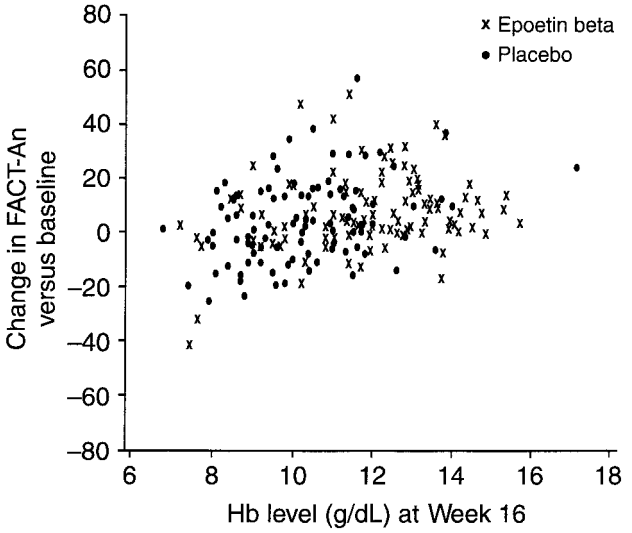

FIGURE 1. Correlation ($P = 0.001$; $r = 0.32$) between change in quality of life (QOL; measured by the Functional Assessment of Cancer Therapy Anemia [FACT-An] scale) and final hemoglobin (Hb) level in patients ($n = 205$) with lymphoid malignancies treated with epoetin beta for 16 weeks.

whether an increase in Hb concentration or the achievement of a fixed target Hb level (i.e., 12 g/dL) should be recommended in the writing of clinical guidelines for the use of erythropoietic agents to maximize QOL benefits for anemic patients with cancer.

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We find ourselves in substantial agreement with our respected colleagues Drs. Brandberg and Österborg. Anemia is indeed common in patients with cancer, and therapy to treat that anemia is associated with substantial improvements in quality of life (QOL). In addition, we agree and have previously published that the magnitude of the improvement in QOL is significantly correlated with the magnitude of the increase in hemoglobin concentration. An increase of 2 g/dL is associated with a measurable improvement in mean QOL; an increase of 3 or 4 g/dL is associated with a mean QOL improvement that is not only measurable but greater than the improvement associated with a 2 g/dL increase. For the purposes of good patient care and development of anemia treatment guidelines, we agree that once the patient is symptomatically anemic, increasing the hemoglobin level is the most important and best-established objective.

Our analysis of a relatively large data set was intended to address a somewhat different issue. The prevailing belief among cancer specialists has been that severe anemia is symptomatic and mild and moderate anemia (hemoglobin concentration $>$ 8 g/dL and $<$ 12 g/dL) is relatively asymptomatic. This paradigm suggests that patients with an increase of 3–4 g/dL experience a greater mean increase in QOL than do patients with a 1–2 g/dL increase, because patients in the former category are more likely to have been severely anemic, and therefore symptomatic, at baseline. The underlying assumption is that, when graphed, the line relating QOL to hemoglobin concentration for a population of patients with cancer does

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not have a constant slope over the full range of hemoglobin levels encountered in oncology; the line is predicted to be steeper at lower hemoglobin levels. Therefore, our observation that the slope became steeper as hemoglobin levels increased within the mild anemia range (hemoglobin concentration $>$ 10 g/dL and $<$ 13 g/dL) compared with the moderate anemia range (hemoglobin concentration $>$ 8 g/dL and $<$ 10g/dL) was unexpected. Stated another way, our data suggest that a given increase in mean hemoglobin concentration does not necessarily result in the same mean increase in patient QOL over the range of baseline hemoglobin concentrations; specifically, the mean increase is greater in the mild range than in the moderate range. This finding has important implications that extend beyond the established benefit of increasing hemoglobin levels in anemic patients with cancer.

Our results have not been reported previously or observed in randomized clinical trials. Drs. Brandberg and Österborg are correct in pointing out that QOL changes in patients receiving cancer chemotherapy are complicated by a high degree of interindividual variability, both in terms of baseline values and change scores. In our analysis, this variability was offset by a large patient sample size ($n > 4000$), which we believe allowed us to demonstrate the correlation between mean QOL gain for a given hemoglobin increment and baseline and final hemoglobin concentrations. Because these sample sizes are not available in individual randomized controlled trials, it was necessary for us to use the retrospective approach to a pooled data set.

Based on the literature cited by our colleagues, the goal of anemia therapy should be to increase hemoglobin concentration to produce established QOL benefits; however, the existing literature does not address important questions. At what level of hemoglobin should the clinician suspect that the anemia is compromising functional status or contributing to a patient's reported fatigue? If a patient is becoming anemic during chemotherapy and the hemoglobin level is expected to decrease further, at what level should therapy be initiated? And finally, if a patient is responding to therapy both in terms of hemoglobin level and QOL/fatigue status, at what hemoglobin level should the therapy be held? The results of our study suggest some answers. Because mild anemia contributes disproportionately to fatigue, therapy started early, at higher hemoglobin levels than earlier data would have supported, should optimize QOL; 12 g/dL is a reasonable hemoglobin level to aim for in a responding, benefiting patient.

Consider a hypothetical patient who began recombinant erythropoietin therapy with a hemoglobin level of 8 g/dL and severe fatigue and now has a hemoglobin level of 10 g/dL and is still fatigued but improving. We assume that Drs. Brandberg and Österborg would believe that this patient should be treated with the goal of achieving either complete relief or a hemoglobin level of at least 12 g/dL (whichever occurred first) and not held at a hemoglobin level of 10 g/dL simply because a target increase of 2 g/dL was achieved. If this assumption is true, then there is no disagreement here.

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Predictive Factors for Suicidal Ideation in Patients with Unresectable Lung Carcinoma

A 6-Month Follow-Up Study

In an interesting article, Akechi et al.[1] reported on predictive factors for suicidal ideation in patients with unresectable lung carcinoma. The results of their multivariate analyses indicated that pain at baseline and the development of depression were significant predictive factors.

The purpose of this letter is to point out to the readership that these results support and are supported by previous data from the general medical literature, the chronic pain literature, and the cancer/pain literature. This literature is as follows. The vast majority of completed suicides in cancer patients occur among those patients with inadequately controlled or poorly tolerated severe pain.[2] Similarly, suicide ideation in human immunodeficiency virus (HIV)-infected ambulatory patients was found to be highly correlated with the presence of pain.[2] Patients with multiple sclerosis frequently report pain. These patients have a twofold increased suicide risk.[3] Migraine headache sufferers also have been shown to be at increased risk for suicide attempts.[4]

It also appears that there is a high incidence of suicidal ideation among patients suffering from chronic nonmalignant pain. In a survey of members of a chronic nonmalignant pain self-help organization, approximately 50% of the respondents reported that they had considered suicide.[5] Chronic pain patients

with "central"pain that is due to a lesion in the central nervous system also are at increased risk for suicide completion.[6]

Among chronic pain patients, the development of suicidal ideation is time-dependent. The longer the pain duration, the greater the likelihood of the presence of current suicidal ideation.[7] In a pain facility study, Fishbain et al.[8] demonstrated that chronic pain patients' age-associated suicide completion rates were significantly greater than those of the general population and raised the issue of whether chronic pain was a suicide risk factor. Finally, in a recent study, Penttinen[9] reported on an unexpected association between back pain and suicidal tendency in Finnish farmers.

The Penttinen study was designed to investigate the relation between back pain and fatal myocardial infarction. However, subjects reporting back pain during the year before study baseline had a significantly increased risk of committing suicide during the first 10 years of follow-up compared with subjects with no back pain symptoms. When adjusted for age, this finding remained significant. The above data would indicate that any patient groups, including those with cancer, are at risk for suicide ideation and suicide completion if chronic uncontrolled pain is present.

A final issue is the question of the underlying reason(s) for the association between pain and suicide completion. Here, the strongest evidence relates to the association between pain and depression. The prevalence of depression has been demonstrated to be higher in chronic pain patients with nonmalignant pain versus nonchronic pain patients.[10] In addition, depression appears to share a unique variance with pain[2] and more severe pain is reportedly associated with more severe depression.[12] There also is some evidence that links pain, depression, and suicide. Here, Stenager et al.[13] found that suicide attempters who reported pain were depressed more often than suicide attempters without pain. In addition, in a follow-up section of the study, a logistic regression analysis demonstrated that painful somatic disease and depression were independent predictors of completed suicide. Consequently, each could be a suicide risk factor.

A diatheses-stress framework has been proposed to conceptualize the development of depression in patients with chronic pain.[14] However, it still is being debated whether depression is an antecedent or consequence of chronic pain.[15,16]

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We read the letter from Dr. Fishbain with great interest and acknowledge his informative findings regarding an association between chronic nonmalignant pain and suicidal ideation, suicidal attempt, and suicide completion. We agree with his comments that the suicidal tendency in cancer and noncancer patients has certain features in common, such as a significant relation between persistent uncontrolled pain and suicidal ideation and suicide completion.

We would like to add several findings regarding pain, depression, and suicidal ideation and suicide completion from previous reports on cancer. Hietanen et al. investigated the difference between cancer patients who had committed suicide and other patients who had committed suicide and found that approximately 75% of the cancer suicide patients had uncontrolled pain and that the cancer patients had a greater degree of pain.[1] Henriksson et al. reported that 80% of cancer suicide patients had depressive disorders.[2] Chochinov et al. investigated associations between desire for death, pain, and depression in terminally ill cancer patients and suggested that depression may be closely related to desire for death in a causal pathway, whereas pain may exert a more indirect effect (prolonged pain may lead to depression followed by desire for death).[3,4] However, the results of our study demonstrated that pain is an independent predictive factor of suicidal ideation in patients with newly diagnosed, advanced lung carcinoma.[5] Furthermore, our previous study investigating background differences among cancer patients who were referred for psychiatric consultation because of depression with or without suicidal ideation indicated that poor physical functioning and severe depression, but not pain, were risk factors for suicidal ideation.[6] These findings indicate that both pain and depression are closely associated with suicidal ideation and suicide completion in cancer patients; however, no causal relations between pain, depression, and suicidal ideation and suicide completion are clear in this population. Because the causality remains controversial in both cancer and noncancer patients, further studies are needed to clarify the complicated relations among pain, depression, and suicide-related issues, including suicidal ideation and suicide completion.

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