Correlation Between Hemoglobin and Fatigue in Women Undergoing Adjuvant Chemotherapy Without Erythropoietin-Stimulating–Agent Support

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Abstract

Background—Fatigue is a common complication of adjuvant chemotherapy and compromises the quality of life of breast cancer survivors. We sought to correlate serial hemoglobin (Hb) levels with fatigue in a population of women on adjuvant chemotherapy, none of whom received erythropoietin-stimulating agents or red blood cell transfusions.

Patients and Methods—Seventy-five women participated in a study using quality-of-life questionnaires to assess changes in need for psychosocial support over time. Questionnaires were administered within 30 days of initiating adjuvant therapy and at 2, 6, and 12 months. Fatigue was assessed by the 36-Item Short-Form Health Survey (SF-36). Hemoglobin levels at each time point were captured retrospectively. Complete data are included for 40 of the 46 women who received adjuvant chemotherapy. Paired-samples *t* tests were conducted to compare mean SF-36 Energy/ Fatigue scores between time points, and independent-samples *t* tests were conducted for comparisons against norms. Simple correlations (Pearson *R*) were conducted between SF-36 variables and Hb levels at each time point.

Results—At 2 months, 23.4% of women had Hb < 11 g/dL compared with 12.9% at 12 months. Compared with norms for women in the general population and breast cancer survivors, these women reported worse fatigue at baseline and at 2 and 6 months. A strong linear relationship was observed between Hb at 2 months and SF-36 Energy/Fatigue scores at 12 months ($r = 0.71$; $P = .002$).

Conclusion—Participants with high fatigue at 12 months had Hb levels at 2 months 13% lower than those with low fatigue. This finding suggests that chemotherapy-induced decline in Hb might be a marker of physiologic reserve.

Keywords

Physiologic reserve; Quality of life; Role limitations

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Introduction

Fatigue is commonly reported by women undergoing treatment of early-stage breast cancer and significantly compromises quality of life (QOL).[1-3] The relationship between fatigue and anemia has been difficult to establish.[4] Cancer treatment, depression, menopause, and sleep disruption also contribute to fatigue in this population.

We undertook a trial to serially assess changes in psychosocial needs over time in a population of women with early-stage breast cancer who were receiving adjuvant chemotherapy. A battery of questionnaires was completed at baseline and serially over 1 year and included the 36-Item Short-Form Health Survey (SF-36) Energy/Fatigue subscale. None of these women received erythropoietin-stimulating agents (ESAs) or red blood cell transfusions. Thus, we sought to determine the effect of hemoglobin (Hb) levels on fatigue, unconfounded by treatment of anemia.

Patients and Methods

Participants

Patients from the medical oncology clinics at Washington University in St. Louis, MO, were approached for participation in a trial on clinical and psychosocial factors of QOL in breast cancer. Women were considered eligible if they were within 30 days of initiation of adjuvant chemotherapy for stage I or II breast cancer, had an Eastern Cooperative Oncology Group performance status of 0 or 1, and signed a consent form approved by the Institution Review Board of Washington University. Patients were ineligible if they had metastatic disease, were pregnant, or were unwilling to complete serial questionnaires for the study duration.

Seventy-five women with early-stage breast cancer were enrolled in a study addressing psychosocial support for women undergoing adjuvant therapy, and 46 of these women were treated with chemotherapy. The women completed a battery of questionnaires that addressed fatigue, general health-related QOL, and overall psychosocial adjustment to breast cancer at 4 time points during the study: at baseline and at 2, 6, and 12 months after initiation of chemotherapy. Hemoglobin levels were captured retrospectively at 3 time points for 40 of the 46 women treated with chemotherapy. Hemoglobin levels were drawn at the same clinic visit when the questionnaires were completed. No patient received ESAs or red blood cell transfusions during the course of adjuvant chemotherapy.

Measurements

Baseline information was obtained within 1 month of initiating the first cycle of adjuvant chemotherapy. Treatment and demographic information were collected, and measures of psychosocial functioning and QOL were administered. These measures were repeated 2, 6, and 12 months after the start of adjuvant chemotherapy. Hemoglobin levels were assessed at the same time as fatigue levels.

The SF-36 is a measure of health-related QOL that is not disease specific but has been used widely in patients with breast cancer and other chronically ill patients.[5-8] This scale

generates scores on the following 8 subscales: Energy/Fatigue, Physical Functioning, Role Limitations due to Physical Problems, General Health, Bodily Pain, Social Functioning, Role Limitations due to Emotional Problems, and Mental Health Index. Scores range from 0 to 100, with higher scores indicating better health. Energy/Fatigue, General Health, and Mental Health Index are "bipolar" subscales. If no limitations are reported on these bipolar subscales, scores are around the midpoint of 50. Positive QOL states are reflected in scores above 50, and negative QOL states are shown by scores below 50. When comparing scores, 5-point differences are considered clinically meaningful. The SF-36 subscales have been shown to be reliable (Cronbach's $\alpha = 0.75$-0.91) and to have adequate to substantial construct validity in a variety of medically ill populations.[8]

We were interested in the SF-36 Energy/Fatigue subscale as our primary measure of fatigue. There is no generally accepted definition of fatigue, although it is commonly thought to involve feeling tired and weak, with a lack of energy. Like pain, fatigue is nearly always assessed by self-report, and there is no gold standard. Most studies define fatigue by the instrument used for its measurement.[5] The SF-36 Energy/Fatigue subscale assesses both energy ("pep, energy") and fatigue ("worn out, tired") over the past 4 weeks, using a 5-choice verbal rating scale format. This subscale has been shown to be highly correlated with other commonly used measures of fatigue and has distinguished patients with breast cancer from women with benign breast problems.[9,10] It has shown excellent empirical validity and sensitivity to the effect of disease and treatment and has been used as the primary measure of fatigue in various recent studies of breast cancer patients and survivors.[6,10,11] Although there is growing interest in the multidimensional nature of fatigue, the SF-36 Energy/Fatigue subscale is a venerable and still-often-used instrument for assessing fatigue in various normal and patient populations, including patients with breast cancer. For normative comparisons, we included norms for women from the general US population and from a large study (N = 2582) of breast cancer survivors (averaging 2 years after completion of initial treatment).[8,11]

Statistical Analysis

Paired-samples *t* tests were conducted to compare participants' mean SF-36 Energy/Fatigue scores between time points and independent-samples *t* tests for comparisons against norms. Simple correlations (Pearson *R*) were conducted between SF-36 variables and Hb levels at each time point. A more stringent criterion for significance ($\alpha = .004$) was used to control for type I errors. This was determined by dividing the usual α level of .05 by 12 (3 Hb time points $\times$ 4 Energy/Fatigue time points, for a total of 12 simple correlations). Because it would be a major missed opportunity to not examine associations between Hb levels and the other SF-36 subscales at each time point, we conducted exploratory analyses of these relationships using simple correlations ($\alpha = .05$). All analyses were conducted using SPSS version 12.0.2.

Results

Participant characteristics are shown in Table 1. The mean age was 47.7 years (range, 28-70 years), most women (72.5%) were married, and slightly > two thirds were non-Hispanic

white. Approximately one third were employed, nearly one quarter were on medical leave, and 17.5% were retired. Participants had > 2 years of post–high school education on average and a reported mean household income of nearly $55,000. Lumpectomy was performed in 25 patients (63%), and mastectomy was performed in 15 (37%). Thus, the 25 patients who underwent lumpectomy also had adjuvant radiation during the study. The surgical stage was I in 15 patients and II in 25 patients. An average of 5.1 cycles of chemotherapy were administered; 23 patients received 4 cycles, 12 received 6 cycles, and 5 received 8 cycles. At 2 months, 23.4% of patients had Hb < 11 g/dL compared with 12.9% at 12 months. There were no significant associations for Hb levels versus cancer variables (stage, type of surgery, number of cycles of chemotherapy, tamoxifen use) or demographic variables (age, marital status, education, income, hours worked per week); therefore, no covariates were controlled for in subsequent analyses.

Table 2 shows normative comparisons of participant SF-36 Energy/Fatigue scores. The patients' scores at baseline (within 1 month of initiating chemotherapy) and at 2 months were significantly into the "negative QOL" range (< 50). Compared with norms for women in the general population and breast cancer survivors, these participants reported poorer SF-36 Energy/Fatigue scores at baseline, 2 months, and 6 months (all $P < .05$). All of these differences (8.6-15.3 points) exceeded the 5-point criteria for clinical meaningfulness. However, at 12 months, participants' fatigue scores did not differ from either normative group. In addition, changes in Energy/Fatigue scores for these participants at 12 months, compared with scores at baseline and 2 and 6 months, were statistically significant and exceeded the 5-point criteria for clinical meaningfulness ($P < .05$).

Table 3 shows simple correlations between Hb levels and fatigue scores. Hemoglobin levels at 2 months were strongly correlated with SF-36 Energy/Fatigue scores at 12 months ($r = 0.71$; $P = .002$). This linear, dose-response relationship is shown graphically in Figure 1. None of the other relationships were significant. To determine whether Hb levels at 6 or 12 months might explain the relationship between Hb at 2 months and SF-36 Energy/Fatigue at 12 months, a hierarchical regression analysis was conducted. Hemoglobin levels at 6 and 12 months were forced into the model first but did not explain a significant degree of variance in Energy/Fatigue scores (adjusted $R^2 = 0.125$; F = 1.999; $P = .178$). Next, when Hb at 2 months was forced into the model, explained variance increased by 30.4% (adjusted $R^2 = 0.429$; F = 3.916; $P = .027$). We also examined whether Hb at 2 months would explain the change in fatigue from 2 to 12 months by controlling for Energy/Fatigue scores at 2 months. Energy/Fatigue at 2 months was not a significant predictor of Energy/Fatigue at 12 months (adjusted $R^2 = 0.163$; F = 3.916; $P = .068$). However, when scores for Hb at 2 months were entered, the model became significant (adjusted $R^2 = 0.487$; F = 8.129; $P = .005$). In addition, we compared Hb levels at each time point for women with high (SF-36 Energy/Fatigue > 50) versus low (SF-36 Energy/Fatigue 50) fatigue at 12 months. No differences were observed for Hb at 6 or 12 months. However, the high-fatigue group at 12 months had lower Hb at 2 months than the low-fatigue group (13.3 g/dL vs. 11.8 g/dL; $P = .032$).

In exploratory analyses, we examined associations between Hb levels and the remaining SF-36 subscales. Significant relationships were observed for Hb levels at 6 months versus Role Limitations due to Physical Problems at 6 months ($r = 0.44$; $P = .035$) and Hb levels at

12 months versus Role Limitations due to Emotional Problems at 12 months ($r = 0.54$; $P = .04$).

Discussion

Our study includes a homogeneous population of women with early-stage breast cancer undergoing adjuvant chemotherapy, none of whom received ESAs or red blood cell transfusions. When compared with normative data from the general population and breast cancer survivors, fatigue in our patients was significantly poorer at baseline, 2 months, and 6 months. Indeed, mean fatigue scores for these women at baseline (within 1 month of initiating chemotherapy) and at 2 months were significantly into the "negative QOL" range. Patients were actively undergoing systemic therapy at these times and were expected to be more fatigued. That average fatigue scores at 12 months were identical to norms supports our contention about the role of active therapy contributing to fatigue.

We identified a significant relationship between Hb levels at 2 months and fatigue at 12 months. Despite the relatively small number of women included in this data set, the relationship was strong and consistent across the range of Hb levels, as shown in Figure 1. In addition, this association remained robust after controlling for subsequent Hb levels or fatigue at 2 months. After dividing the women into high- versus low-fatigue groups at 12 months, the groups differed on Hb levels only at 2 months. In fact, the group that would experience high fatigue at 12 months met current American Society of Clinical Oncology criteria for erythropoietin therapy at 2 months (mean Hb levels < 12 g/dL). Hemoglobin levels seemed to presage fatigue by 10 months in this study.[12]

We are uncertain about why we found a lack of contemporaneous links between Hb and fatigue across all time points. One possible explanation involves restriction of range for SF-36 fatigue at the earlier time points. Fatigue scores are lower and somewhat more tightly distributed at baseline through 6 months. It is only at 12 months that mean fatigue scores normalize and the distribution increases. That is, fatigue across the patients in this study was greater before the 12-month time point. Thus, early anemia might be indicative of fatigue levels only after fatigue scores have normalized at 12 months for those who did not have low Hb levels at 2 months.

Erythropoietin alfa was approved for patients with cancer by the US Food and Drug Administration on the basis of a demonstrated reduction in need for red blood cell transfusions during chemotherapy. However, the ESAs have not been shown to decrease fatigue or improve QOL in double-blind, placebo-controlled trials.[13] Also, the use of ESAs in women with breast cancer might have adverse consequences. A randomized, double-blind, placebo-controlled trial testing the role of erythropoietin alfa was conducted in 939 women with metastatic breast cancer receiving chemotherapy. Although the primary endpoint of study was 1-year survival, the trial was stopped early because of an adverse outcome for patients receiving the ESA. Women assigned to the treatment arm had significantly shortened 1-year survival compared with the control group (70% vs. 76%; $P = .0117$). Shortened survival was attributed to both an increase in disease progression and

thromboembolic complications in those receiving the ESA.[14] Such data contributed to restriction on the use of ESAs in chemotherapy-induced anemia.[15]

Earlier clinical trials that have addressed fatigue and anemia generally followed up patients for < 6 months,[13] yet breast cancer survivors consistently report fatigue years after completion of therapy and without evidence of recurrent cancer. We raise the possibility that the "stress" of adjuvant chemotherapy identifies a group of women who have a compromised "physiologic reserve." By that, we mean they are physiologically older than their chronological age. In the geriatric population, anemia is an independent prognostic factor that correlates with shortened survival and predicts for hospitalizations.[16-18] In the geriatric setting, Hb might be a marker for distinguishing physiologic age from chronologic age.[19,20] Alternatively, one might consider that periods of sustained anemia produce hypoxia on normal tissues, and that can produce long-term effects on the body's functional reserve, manifesting as fatigue.

Our study has a number of limitations. Because this study relied on a convenience sample, our findings might not be applicable to the general population of patients with breast cancer. Participants were accrued to the study after their surgical treatment and before the start of chemotherapy; we do not have Hb samples before surgical treatment. Although radiation therapy produces less fatigue that chemotherapy, it does cause fatigue, and 63% of women received radiation treatment during the 6-month time points. However, the 12-month fatigue levels should not be affected by radiation therapy. Another important limitation deals with sample size and statistical power. It is quite possible that the lack of significant relationships between Hb and fatigue at other time points is due to insufficient power. Therefore, this statistical limitation must be given consideration in the interpretation of these findings until a study with greater power can confirm or disconfirm these findings.

Conclusion

In summary, despite these limitations, the results raise the possibility that a decline in Hb after chemotherapy is a marker of physiologic reserve, independent of age. Further studies to test this hypothesis are warranted.

Acknowledgments

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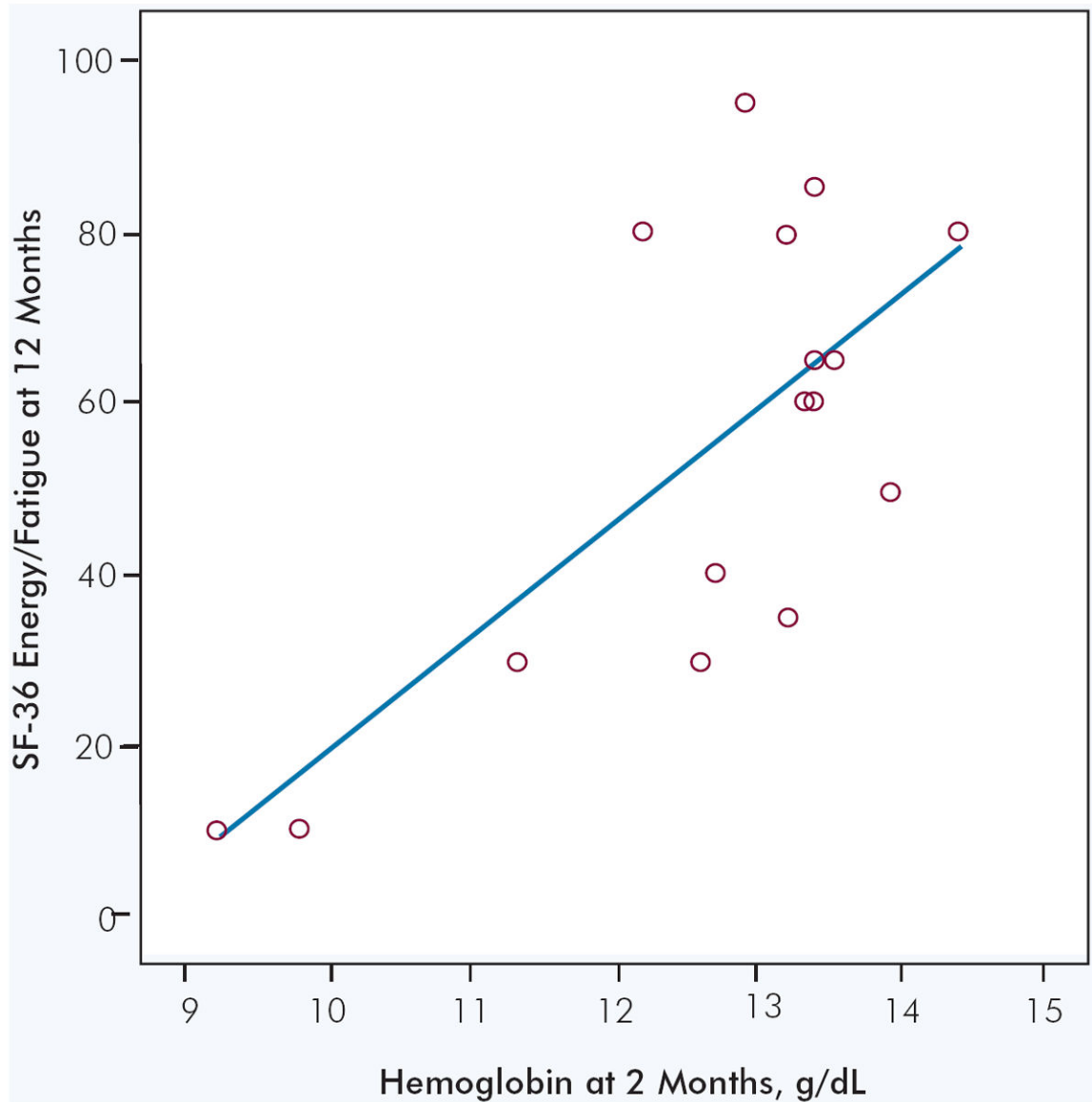
Figure 1.
Scatter Plot of Relationship Between Hemoglobin at 2 Months and SF-36 Energy/Fatigue at 12 Months

$r = 0.71$; $P = .002$; n = 16. Each circle represents 1 patient.

Abbreviation: SF-36 = 36-Item Short-Form Health Survey

Table 1

Participant Characteristics

Characteristic	Value
Number of Patients	40
Age (Years)	47.7 ± 10.1
Race/Ethnicity, n (%)	
Non-Hispanic White	27 (67.5)
African American	11 (27.5)
Asian-American	1 (2.5)
Other	1 (2.5)
Marital Status, (%)	
Single	2 (5)
Married	29 (72.5)
Divorced	5 (12.5)
Widowed	1 (2.5)
Separated	3 (7.5)
Years of Education	14.3 ± 2.6
Employment Status, n (%)	
Employed	14 (35)
Medical leave	9 (22.5)
Retired	7 (17.5)
Semiretired	1 (2.5)
Unemployed	9 (22.5)
Household Income	$54,850 ± 35,102
Stage of Disease, n (%)	
I	15 (37.5)
II	25 (62.5)
Surgery, n (%)	
Mastectomy	15 (37.5)
Lumpectomy	25 (62.5)
No. of Chemotherapy Cycles, n (%)	
4	23 (57.5)
6	12 (30)
8	5 (12.5)
Tamoxifen, n (%)	
Yes	12 (30)
No	28 (70)
Hb Levels, g/dL	
2 Months	12.3 ± 1.4
Percent with Hb < 11	23.4%

Characteristic	Value
6 Months	12.1 ± 1.3
Percent with Hb < 11	21.2%
12 Months	12.6 ± 1.3
Percent with Hb < 11	12.9%

Data are presented as mean ± SD or number and percentage.

Abbreviation: Hb = hemoglobin

Table 2

Comparison of Participants' SF-36 Energy/Fatigue Scores[*] with Norms for Women from the General Population and Breast Cancer Survivors

Time Point	Participants (n = 40)	General Population Norms[†]	Breast Cancer Survivors (n = 2582)[‡]
Baseline	45.3 ± 19.5[§][‖]	58.4 ± 21.5[§]	58.8 ± 20.9[§]
2 Months	43.5 ± 18.8[§][‖]	58.4 ± 21.5[§]	58.8 ± 20.9[§]
6 Months	49.8 ± 22.2[§][‖]	58.4 ± 21.5[§]	58.8 ± 20.9[§]
12 Months	56.4 ± 25.7[‖]	58.4 ± 21.5	58.8 ± 20.9

Data are presented as mean ± SD.

[*] Higher scores = better health.

[†] Norms for women from the general US population.[11]

[‡] Study by Bardwell et al of health-related quality of life in breast cancer survivors.[8]

[§] Differences for means for participants versus general population and breast cancer survivor norms exceeded the 5-point criteria for clinical meaningfulness and were statistically significant (independent-samples t tests, $P < .05$).

[‖] Compared with scores at 12 months, differences for means for participants at baseline and 2 and 6 months exceeded the 5-point criteria for clinical meaningfulness and were statistically significant (1-sample t tests, $P < .05$).

Abbreviation: SF-36 = 36-Item Short-Form Health Survey

Table 3

Pearson Correlations (*r; P*): Hemoglobin Levels Versus SF-36 Energy/Fatigue

SF-36 Energy/Fatigue	Hemoglobin		
	2 Months	**6 Months**	**12 Months**
2 Months	0.208; .298 (n = 27)	0.253; .213 (n = 26)	0.190; .364 (n = 25)
6 Months	−0.119; .598 (n = 23)	0.329; .135 (n = 23)	0.117; .614 (n = 22)
12 Months	0.712; .002 (n = 16)	0.462; .072 (n = 16)	0.356; .193 (n = 15)

Abbreviation: SF-36 = 36-Item Short-Form Health Survey