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The purpose of this study was to assess whether the previously demonstrated relationship between quality of life and anemia in cancer patients was influenced by gender. Two hundred and fifty one patients of various diagnoses completed the Functional Assessment of Cancer Therapy – Anemia (FACT-An) subscale to measure quality of life. Regression analysis revealed a significant positive correlation between hemoglobin and FACT-An subscale score, as well as a negative correlation between Eastern Cooperative Oncology Group (ECOG) performance status and FACT-An subscale score. Mean comparison demonstrated a significant difference in FACT-An score between patients currently and not currently receiving chemotherapy. An analysis of covariance, controlling for current therapy and ECOG performance status as confounders, found that men score more poorly on the FACT-An within the hemoglobin range of 10.0 – 13.0 g/dL. In conclusion, the normalization of hemoglobin levels improves quality of life; however, gender differences should be taken into account when determining optimal hemoglobin levels.

GENDER DIFFERENCES IN HEMOGLOBIN

LEVEL AT THE ONSET OF SYMPTOMS OF

CANCER-RELATED ANEMIA

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THESIS

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CHAPTER I

INTRODUCTION TO THE STUDY

Patients with cancer often develop anemia secondary to their malignancies or treatment (17). The statistics vary by study, but it appears that possibly one-half or more of all cancer patients will develop anemia at some time (17,31). Traditionally, anemia was diagnosed only as patient hemoglobin levels fell below 8 g/dL, well below the baseline ranges of 12-16 g/dL for females and 14-18 g/dL for males (31). However, recent studies have shown that patients may begin to experience fatigue-related symptoms of anemia at hemoglobin levels between 10 and 12 g/dL (2,4,7,9,17,31,33). Among these symptoms, functional impairment and a decreased sense of well-being are the most commonly reported quality of life factors impaired by anemia (4). This impairment includes a measurably diminished tolerance for exercise, ability to work, and capacity to participate in leisure and social activities (4). These are all factors which cannot be appreciably measured in a general consultation or simply through the monitoring of hemoglobin levels. Thus it has become increasingly important that oncologists consistently measure patient quality of life outcomes in addition to blood counts in order to provide the best supportive care for the patient.

Cancer-related anemia is often a result of a decrease in erythropoietin production (36). When this is the case, the anemia may be treated with

subcutaneous injections of recombinant human erythropoietin. The American Society of Clinical Oncology (ASCO) and the American Society of Hematology (ASH) have developed universal guidelines for the administration of recombinant human erythropoietin (rHuEPO) that do not take into account gender differences, despite the differences in red blood cell mass among healthy men and women.

This study attempts to identify gender-based differences in quality of life outcomes in cancer patients with anemia. The patient population includes cancer patients seen in the Weatherford, Mineral Wells, and downtown Fort Worth offices of Texas Cancer Care. Each patient was asked to complete the Functional Assessment of Cancer Therapy-Anemia (FACT-An) subscale questionnaire and to evaluate their Eastern Cooperative Oncology Group (ECOG) performance status. FACT-An scores were correlated with hemoglobin level and ECOG performance status to examine the strength of the linear relationship. Age and current therapy were also statistically analyzed for a possible role in the patient perception of quality of life. Finally, gender was considered as a possible variable that could alter the hemoglobin to FACT-An score relationship. Examining the role of various categorical predictors on FACT-An score reveals the presence or absence of a statistically significant difference in quality of life scores for men and women at equivalent hemoglobin ranges. These findings may suggest altering the universal application of ASCO/ASH rHuEPO guidelines in favor of a more individualized approach to anemia management.

Problem

Clinicians are beginning to understand that the consequences of cancer-related anemia are detrimental to all facets of the patient quality of life (QOL) (35). By managing anemia with supportive therapy, clinicians can see significant increases in patient functional capacity and overall QOL. The availability of rHuEPO has made anemia-management easier and safer than transfusion; however, the most efficacious methods for rHuEPO usage in anemia-management have yet to be clearly demonstrated experimentally.

In 2001, ASCO and ASH developed clinical practice guidelines for the use of rHuEPO in cancer patients based on an analysis of data published through 1999. These guidelines suggest that anemia-management with rHuEPO begin as patient hemoglobin concentration falls below 10.0 g/dL and that rHuEPO dosages be titrated as levels approach or exceed 12.0 g/dL. These guidelines are based solely on the usage of epoetin to reduce the risk of transfusion, as the panel did not believe that enough evidence existed to support epoetin usage for QOL benefits. Since that time, many studies have shown QOL outcomes to increase concurrently with hemoglobin levels during rHuEPO therapy (1,7-9,13,16,33,35). This new wealth of data suggests that the current guidelines will be altered in the future to include epoetin usage for QOL benefit. However, the current data do not account for possible gender differences in hemoglobin level at the onset of anemia. Gender differences in hemoglobin level at the onset of symptoms and in

the severity of symptoms at equivalent hemoglobin levels must be determined prior to the establishment of comprehensive guidelines for epoetin usage for QOL benefit.

Hypothesis

As no previous trial has examined differences in anemia-related QOL outcomes due to gender, the present study will look for significant gender differences in the level of fatigue, at varying hemoglobin ranges, to determine if special considerations should be taken for gender-based anemia management. The overall hypothesis is that male cancer patients will begin to exhibit anemia-related symptoms before female patients when QOL is measured at equivalent hemoglobin levels. The possibility of a difference in QOL outcomes due solely to gender seems likely due to differences in baseline hemoglobin concentrations in men and women. As healthy men generally have a greater hemoglobin concentration than their female counterparts, it is expected that they will exhibit symptoms of anemia, especially fatigue, at proportionally greater hemoglobin levels than women. It follows that when examining men and women at equivalent, non-baseline hemoglobin ranges, men should score more poorly on the FACT-An subscale. This study evaluates the QOL of male and female cancer patients at various hemoglobin ranges to verify if such differences exist.

Significance

The devastating impact of anemia on the quality of life of cancer patients is well-documented and many studies have shown an increase in QOL following the treatment of anemia. In a survey administered by *Curt et al.* to 379 cancer patients, 91% reported that fatigue prevented them from having a "normal life" (10). It is imperative that clinicians provide the optimal treatments for management of anemia in order to provide their patients with a "normal" approximation of their former lives. Significant data do not exist to support the standard of care currently supported by ASCO and ASH. This analysis considered only those data published through 1999, and thus concluded that while epoetin therapy significantly diminished the need for transfusion, there were not enough data to support the QOL benefit from epoetin therapy. Since this report, data from prospective trials indicating the correlation between anemia and QOL have become available. These trials have demonstrated improvements in patient QOL following anemia management, and the need to refine current treatment guidelines (1,7-9,13,16,33,35). Based on results of two open-label, community-based trials, *Crawford et al.* suggested that the ASCO/ASH regulations be replaced with a more individualized approach that requires the monitoring of hemoglobin, symptoms of anemia, and QOL (9).

The objective of this study is to determine if gender should be taken into consideration when establishing the proper levels for initiation of epoetin treatment and titration of epoetin dosage. Further, this trial will provide data on

the usage of the FACT-An subscale alone, without the general component, as a measure of patient fatigue. A significant correlation of FACT-An score with hemoglobin may indicate that the subscale is appropriate for usage by healthcare providers as a brief assessment of fatigue.

CHAPTER II

BACKGROUND

Anemia and Cancer

Anemia is defined as a deficiency in the amount of circulating hemoglobin or the number of red blood cells, and it has been found to occur in over 50% of patients with malignancies (26). The prevalence of anemia in patients with cancer may be due to the underlying disease, radiation treatments, or chemotherapy. Chronic disease contributes to anemia as the immune system responds to the tumor by producing an overabundance of cytokines, such as interleukin-1 and tumor necrosis factor-α. These and other cytokines alter renal production of erythropoietin, diminish receptor response to erythropoietin, decrease the lifespan of erythrocytes, and impede the utilization of iron (17,36). Cancer-related blood loss may further induce anemia. In addition, chemotherapy also contributes to anemia by diminishing erythropoietin production and destroying hematopoietic stem cells, while radiation therapy may directly damage bone marrow (17). Lastly, nausea induced by these treatments may provoke nutritional deficiencies which prevent red blood cell production (17).

Until recently, only severe anemia was treated, generally by transfusion. Mild to moderate anemia went largely untreated due either to the physician's

guardedness regarding the associated risks of transfusion or to a lack of knowledge regarding the consequences of even mild anemia (35,21). Recent studies have countered this misconception, revealing the influence of anemia on QOL. *Cella et al.* found functional impairment in all cancer patients whenever hemoglobin levels dropped below 12 g/dL (4). Other nonrandomized studies have concurred with the findings of the Cella study regarding the negative impact moderate anemia has on QOL (4,13,16). However, none of these previous studies have evaluated gender as an independent predictor of QOL. Symptoms of anemia include fatigue, dyspnea, tachycardia, dizziness, depression, a decreased libido and appetite, nausea, and sleep disorders (17). The severity of these symptoms is directly related to the degree of the anemia, but varies according to the individual (17). Among these, the most common complaint of anemic patients is fatigue (17,31). Management of anemia reduces fatigue thereby increasing the quality of life in patients undergoing cancer treatment (1,4,13,16,25).

There are also some data that suggest that anemia may have a negative impact on the survival rate of patients undergoing radiation therapy (19,23). For example, *Lee et al.* found that of 451 patients receiving radiation therapy for Stage III or IV head and neck cancer, there was a 15% increase in survival rate for those patients whose anemia was managed (23). Anemia was also found to be associated with lower local-regional control in these patients, which may result in distant metastases or a decrease in survival. It is unknown exactly how anemia may contribute to mortality in patients with cancer, but it is hypothesized that

hypoxia may reduce the radiosensitivity of tumor cells (17). A quantitative analysis in 2001 of 60 studies that measured survival rate and hemoglobin levels of cancer patients found a 65% increased mortality rate for anemic patients, though this rate fluctuated based on tumor type (3). While these data are not definitive, they suggest there may be more reason to manage anemia in cancer patients than just for quality of life benefits.

Erythropoietin

Until the 1990s, blood transfusion was the only available method for managing anemia (30). It was an imperfect method for treating anemia as it decreases the patient's quality of life and has several associated risks, including immunosuppression, infection, and alloimmunization (17,31). In addition, many patients refuse transfusion due to personal or religious beliefs (17). These difficulties prompted researchers to seek other methods to stimulate red blood cell production. They began by attempting to extract erythropoietin from the urine, but it could not be isolated in significant amounts. However, once the gene for erythropoietin was identified, it was then cloned and expressed in cells in culture so that viable quantities of this rHuEPO were produced (47). Recombinant human erythropoietin is virtually identical to endogenous erythropoietin and, therefore, offers the benefits of transfusion without the associated risks (36).

Erythropoietin is one of the few hematopoietic growth factors with a mechanism like that of a hormone (36). It is produced only in response to hypoxia and some studies claim that its production is not influenced by age, gender, or its current plasma concentration (15,29). An abundance of O_2 can limit, but cannot completely arrest erythropoietin production. Hyperviscosity may also limit production (36).

Erythropoietin promotes the proliferation and differentiation of erythroid progenitor cells, thereby regulating the number of erythrocytes in the peripheral blood (44). There is a wide range of what are considered "normal" erythropoietin levels (4 – 26 mU/mL), and there is no gender-based difference in this range (36). There is, however, a difference in the normal red blood cell mass between men and women (4.7 – 6.1 million cells/μl in males vs. 4.2 – 5.4 million cells/μl in females), so other factors, which may include iron stores and androgens, must mediate erythropoiesis. Plasma erythropoietin level will generally not exceed its normal range until hemoglobin is less than 10.5 g/dL (36).

In adults, erythropoietin is produced mainly in the peritubular fibroblastoid cells of the renal cortex, but there is also a contribution from the hepatocytes and fibroblastoid interstitial cells in the liver (36). Fetal erythropoetin is produced solely in the liver (36). The erythropoietin receptor is in the same cytokine receptor family as the receptors for the interleukins, GM-CSF, granulocyte colony-stimulating factor, GH, and prolactin (44). Under a state of hypoxia, the erythropoietin receptor dimerizes with an identical receptor forming

a homodimer (45). With the receptor now activated, the JAK-2 tyrosine kinases associated with each monomer of the receptor undergo crossphosphorylation. The tyrosine kinase then phosphorylates the erythropoietin receptors on tyrosine residues. This creates docking sites for STATs (signal transducers and activators of transcription) that are subsequently phosphorylated by JAK-2 tyrosine kinases. The STATs then dissociate from the receptor and dimerize via SH2 domains before migrating to the nucleus to promote transcription of the erythropoietin gene (42).

Erythropoietin interacts with surface receptors on the erythroid progenitor cells in the bone marrow to promote proliferation and maintain viability (36,44). The early burst-forming unit erythroid cells terminally differentiate into the colony-forming unit erythroid cells in the presence of erythropoeyin and IL-3. The colony-forming unit erythroid cells then require a high concentration of erythropoietin to become a pronormoblast. During the normoblast stage hemoglobin is synthesized, organelles are lost, and finally the nucleus is ejected to form a reticulocyte (36,44).

Management of Anemia with rHuEPO

In 1997, ASCO and ASH began to develop evidence-based clinical practice guidelines for the use of recombinant human erythropoietin in cancer patients. A proposal was submitted to the Agency for Healthcare Research and

Quality (AHRQ) and the Blue Cross Blue Shield Association Technology Evaluation Center (TEC) was selected to develop an evidence-based report. In late 2000, TEC submitted their report to a panel of experts established by ASCO/ASH. This report examined the outcomes of 22 trials (1,927 patients) comparing the outcomes of anemia management using transfusion versus epoetin. Based on the recommendations of the expert panel, ASCO/ASH released clinical practice guidelines for epoetin usage (30).

This report recommends the usage of epoetin on patients with hemoglobin values below 10 g/dL or on a case-by-case basis for individuals with hemoglobin between 10 and 12 g/dL. Once the patient's hemoglobin reaches 12 g/dL or greater, epoetin dosage is to be titrated. The panel did not believe that enough data existed at that time to support normalizing hemoglobin levels above 12 g/dL (30). This final recommendation was supported by a retrospective analysis of studies conducted by *Glaspy et al.* and *Demetri et al.* that found the greatest gains in QOL scores occurred when hemoglobin was raised from 11 to 12 g/dL (10). Furthermore, four studies which enrolled patients with hemoglobins greater than 12 g/dL found no significant improvement in QOL after epoetin treatment (12,37,39,40). However, two open-label, community-based studies published in 2002 found increases in QOL scores even as hemoglobin reached 14 g/dL, though the rate of increase began to slow after 12 g/dL (10). All of these studies were conducted with mixed populations, but failed to specifically examine the impact gender may have on the symptoms of anemia

Despite its demonstrated effectiveness, there are several complications involved with the use of rHuEPO for anemia management. Administration of rHuEPO depletes iron stores as they are used in red blood cell production. Many patients require concurrent administration of iron; however, oral iron may cause nausea and diarrhea, and intravenous iron may result in nausea, fever, dizziness, flushing, headache, or anaphylactic-like reactions in some patients. There are also uncertainties concerning the best hemoglobin levels to initiate and terminate rHuEPO treatment and whether gender differences in response exist. Due to varying individual responses to erythropoietin, it is recommended that the physician closely monitor hemoglobin and quality of life in order to provide an individual assessment. Lastly, only 50-60% of all patients respond to rHuEPO, and there are currently no known effective predictors of the erythropoietin-sensitive patient population (17).

QOL

Cancer treatment is approaching a period when determination of the success or failure of a given therapy must be based upon more than just safety, efficacy, effectiveness, and cost. Even when patients do not have the opportunity to gain traditional benefits such as disease-free survival, they may still enjoy an improvement in QOL as a result of treatment (2). Quality of life is a subjective term that has proven to be as controversial to measure as to define. It has been

defined as the state of well being that is a composite of two components: the ability to perform everyday activities that reflect physical, psychological, and social well-being; and patient satisfaction with levels of functioning and control of the disease (18). Other literature has defined QOL as the patient perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns (41). Despite an inability to accurately phrase what domains are encompassed by QOL, it remains an important variable that not only allows physicians to make comparisons between treatments of similar efficacy, but also to make decisions about future treatments (5).

More clinicians are finding that maintaining QOL is an important aspect of patient care (28,46). An awareness survey conducted by *Tanaka and Gotay* in 1998 showed that most clinicians considered QOL to be just as important as patient survival (38). The positive effect QOL assessment has on treatment was demonstrated in a study by *Detmar and Aaronson* involving 18 patients and six clinicians. They measured the QOL of each patient and provided the results to their physician prior to consultation. Both the patients and physicians agreed that the consultation was more satisfying, and patients emphasized that the doctors seemed to show a greater understanding (14). Nevertheless, despite growing evidence supporting the assessment of QOL, these study results are not translated into the clinical setting. In 1998, *Morris et al.* conducted a survey that revealed that 80% of oncologists supported collecting QOL data during patient

consultations; however, the same survey showed that only 50% of these oncologists actually collected QOL data (27). As awareness is not an impediment to including the collection of QOL data within the standard of care, the primary obstacles may be a lack of time and available resources. It is important that physicians have an available instrument for the collection of these QOL data that accurately measures outcomes and is both brief and easy to administer.

FACT-An

QOL must be measured by addressing specific domains, not by simply asking the patient general questions about their personal perceptions (2). A vague line of questioning will likely result in equally vague answers that will be difficult to measure. A comprehensive measure of the quality of life must include the following four components: physical well-being, functional well-being, emotional well-being, and social well-being (5).

The Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System consists of a 250 question item bank that covers each of these domains (6). The core questionnaire, the Functional Assessment of Cancer Therapy-General (FACT-G) measures overall QOL, and it may be supplemented with additional questions specific to certain conditions (5). An instrument available to specifically measure anemia-related symptoms in cancer patients is the FACT-Anemia subscale (5). The FACT-An is a subscale created by

extensively interviewing fourteen cancer patients and five experts in hematology/oncology (43). The FACT-An actually consists of the thirteen question FACT-Fatigue subscale with an additional seven non-fatigue based questions (5). When administered concomitantly with the FACT-G questionnaire, patients are asked a total of 47 questions (5).

The FACT-An subscale has proven to be both reliable and valid. After its creation, the FACT-An was validated with a cohort of 50 patients (43). The FACT-An demonstrated good stability ($r=0.87$) and internal consistency ($\alpha=0.96$) (5). The questionnaire also showed a strong test-retest reliability coefficient ($r=0.90$) when patients were asked the same questions as before, three to seven days after initially completing the survey (4,5). The survey was negatively correlated with measures of vigor and positively correlated with other measures of fatigue (5). The FACT-An demonstrated the ability to successfully discriminate patients based on hemoglobin level where patients with values below 12 g/dL had lower scores than those patients with hemoglobins above 12g/dL (5,17). As the only QOL parameters of interest in this study are those related to anemia and fatigue, it is necessary that the fatigue subscale be able to stand on its own when not administered concurrently with the FACT-G questionnaire. Based on the results of a validation study, *Yellen et al.* state that "because the 13 item scale alone is psychometrically sound, it should prove useful as an independent, brief assessment of fatigue" (43). Therefore, omitting the general QOL component from the questionnaire should not affect data collection.

CHAPTER III

METHODS

Patient Population

The population of this prospective study is composed of patients who attended the Fort Worth, Weatherford, or Mineral Wells offices of Texas Cancer Care for either chemotherapy or a physician consultation. Following informed consent, patients were asked to voluntarily complete an assessment of fatigue questionnaire (FACT-An) at the time of sign-in. Patients were not excluded based on diagnosis, age, current therapy, or any other measurable variable. In total, 323 patients chose to participate. The study was conducted over a five week period beginning August 4, 2003 and ending September 5, 2003.

Data Collection

The questionnaire received first asked the patient to evaluate personal performance status according to the Eastern Cooperative Oncology Group performance scale (see appendix). The patient was then asked to complete the 20 – question Functional Assessment of Cancer Therapy – Anemia

subscale (see appendix) in order to quantify level of fatigue and other anemia related symptoms. Each question has a five point response category (Table 1) and scores range from 0 – 80 with a larger numerical score indicating a greater state of fatigue. This scale has been rigorously tested and validated in previous trials (4,5,17,43). Patients were only asked to complete a single QOL domain, the anemia subscale, omitting the general QOL parameters, as the only symptoms of interest for the purposes of this study were those induced by anemia.

Table 1. Rating Scale for the Functional Assessment of Cancer Therapy

0 – Not at all
1 – A little bit
2 – Somewhat
3 – Quite a bit
4 – Very Much

To maintain patient privacy, completed questionnaires were removed from the attached consent forms and assigned an identification number based on the patient's iKnowMed identification number. Patient data relevant to the study were retrieved from electronic charting software (iKnowMed), associated with the questionnaire score and ECOG performance status, and then entered into a spreadsheet. These data include gender, age, hemoglobin level at the time of participation, diagnosis, current therapy, and whether the patient was currently receiving rHuEPO for anemia management. These variables were tested for a

possible influence on patient FACT-An scores in an effort to determine the effect they might have on cancer-induced fatigue.

Statistical Methods

All graphs were created and data analyzed using Statistica 6.0 software. Univariate analyses to compare the differences in FACT-An scores between those patients currently receiving chemotherapy and those who were not were performed using the independent samples t-test. Linear regression was used to analyze the associations between FACT-An score and hemoglobin level, ECOG performance status, and age. An analysis of covariance (ANCOVA) was used to determine the effect of gender on FACT-An score while eliminating any variables found to have significant correlations with QOL. A p value of less than 0.05 was considered statistically significant.

CHAPTER IV

RESULTS

Demographic Characteristics

Three hundred twenty three patients participated in this study, but only 251 (78%) completed surveys were eligible for analysis. Reasons for omission included improper completion of the patient questionnaire or the lack of a baseline hemoglobin value if the patient had not received a CBC on the day of completion. The demographics for the patient population are summarized in Table 2. Of the 251 patients, 153 (61%) were female and 98 (39%) were male. Ages ranged from 22 years to 90, but the majority of patients (80%) were over 50. In addition, only 28 (11%) participants had a hemoglobin concentration of less than 10.0 g/dL, while the remaining 223 (89%) had hemoglobins of 10.0 g/dL or greater. Those patients currently receiving chemotherapy (n = 114; 45%) were nearly equal in number to those who were not (n = 137; 55%).

The greatest proportion of patients (79%) had solid tumors and a variety of types were represented. These cancers include breast (n = 61; 24%), colon (n = 25; 10%), lymphomas (n = 26; 10%), lung (n = 37; 15%), and other types of solid tumors (n = 48; 19%). Of the remaining patients, 40 (16%) had benign hematologic disorders, and 14 (6%) had malignant hematologic disorders. The

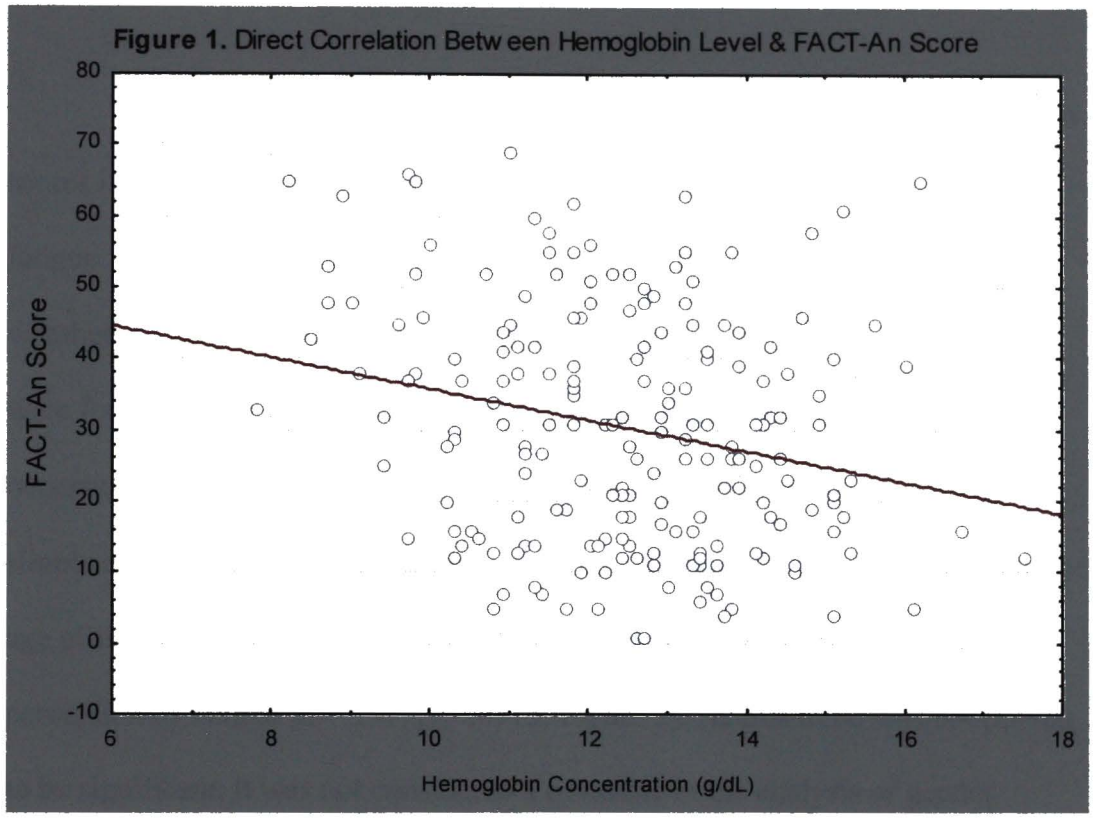
Table 2. Demographic Information of All Responding Patients

Characteristics	Number	Percentage
Total Patients	251	100.0
Gender		
Female	153	61.0
Male	98	39.0
Age Group		
40 and below	19	7.6
41 – 55	50	19.9
56 – 70	113	45.0
71 +	69	27.5
Diagnosis		
Solid Tumors	197	78.5
Breast Cancer	61	24.3
Colon Cancer	25	10.0
Lymphoma	26	10.4
Non-Small Cell Lung Cancer	25	10.0
Small Cell Lung Cancer	12	4.8
Other Solid Tumors	48	19.1
Malignant Hematologic Disorders	14	5.6
Benign Hematologic Disorders	40	15.9
Active Chemotherapy		
No	137	54.6
Yes	114	45.4
Hemoglobin Concentration (g/dL)		
Below 10.0	28	11.2
10.0 – 13.0	135	53.8
13.1 +	88	35.1
ECOG Status		
0	69	27.5
1	107	42.6
2	47	18.7
3	25	10.0
4	3	1.2

hematologic disorders were not included in this analysis due to primary effects of the hematologic disease on hemoglobin concentration. Study participants also represented each of the five ECOG performance status groups; however, scores of 0 (n = 69; 28%), 1 (n = 107; 43%), 2 (n = 47; 19%), and 3 (n = 25; 10%) were better represented than a score of 4 (n = 3; 1%).

Relationship Between Hemoglobin Levels & FACT-An Score

Based on the study data, patients with greater hemoglobin levels tend to experience a superior QOL. There exists a statistically significant direct correlation between patient hemoglobin values and FACT-An-determined QOL scores as determined by regression analysis ($n = 197$, $r = 0.23$, $p < .001$; Figure 1). This modest correlation coefficient is similar to that found by *Crawford et al.* in a similar, but much larger study involving over four thousand patients ($r = 0.27$). These relatively unexceptional coefficients are most likely the result of a nonlinear relationship between hemoglobin levels and QOL, but other variables may also play a role in confounding the correlation. Notably, this study, which involved only the use of the FACT-An subscale, revealed nearly the equivalent correlation as did *Crawford et al.* when using the entire FACT-An questionnaire. These data suggest that the anemia subscale may be utilized alone as a reliable assessment of fatigue.

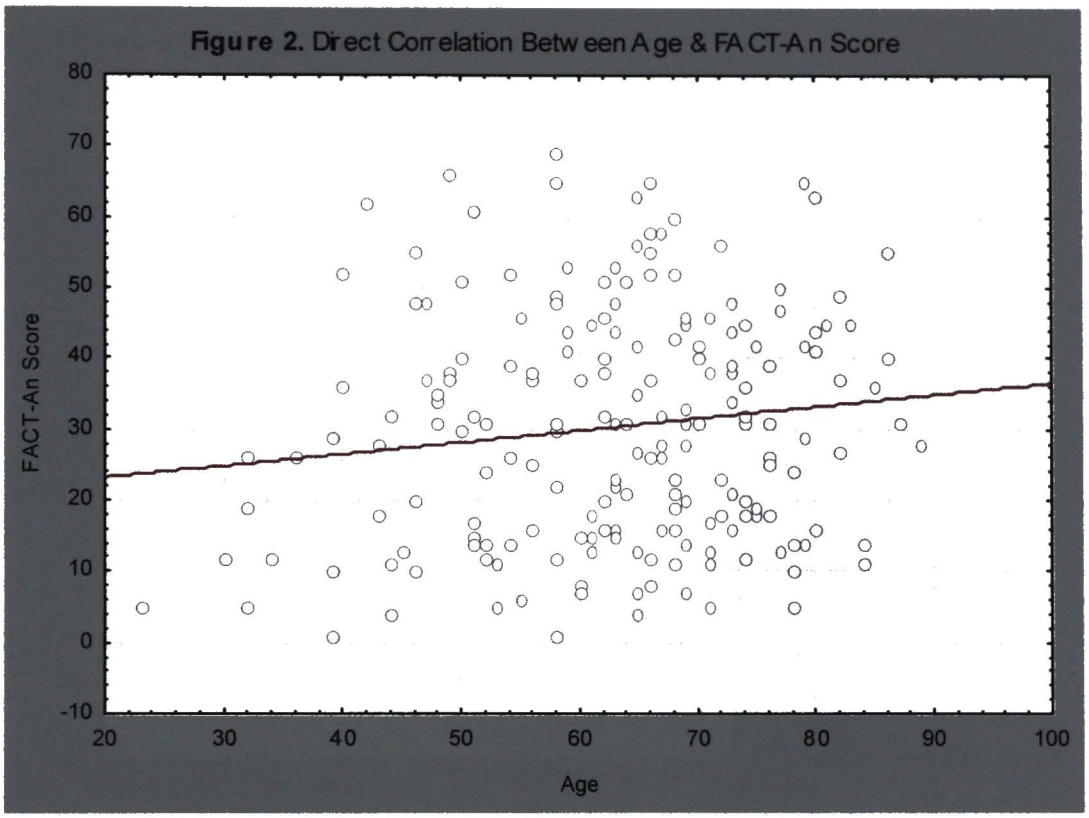


Linear regression analysis of data from all patients with solid tumors revealed a positive correlation between hemoglobin levels and QOL as determined by the FACT-An subscale ($n = 197$, $r = 0.23$, $p < .001$). An increased FACT-An score indicates a greater level of fatigue.

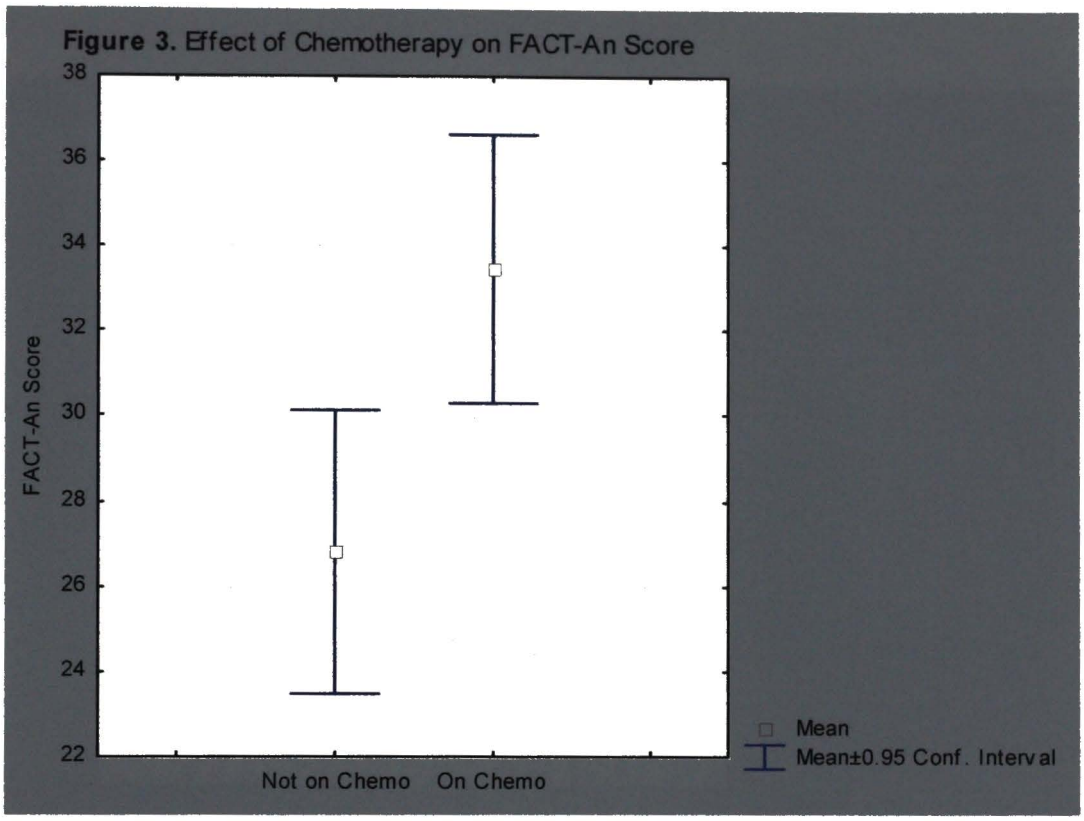
Relationship Between Factors Other Than Gender & FACT-An Score

In order to determine the role of gender in the determination of FACT-An scores it was necessary to examine the correlation of other confounders with fatigue. The confounders measured were age, ECOG performance status, and whether the patient was currently receiving chemotherapy. Those factors that were found to have a statistically significant correlation with FACT-An were necessarily eliminated as covariates during the analysis of gender differences. A simple regression indicates that there is a slight decrease in vigor with age, but the age of the respondent was not found to have a statistically significant effect on perception of fatigue ($n = 197$, $p = .0715$, Figure 2). As this trend was not proven to be significant, it was not considered a covariate in the analysis of gender differences in perception of QOL.

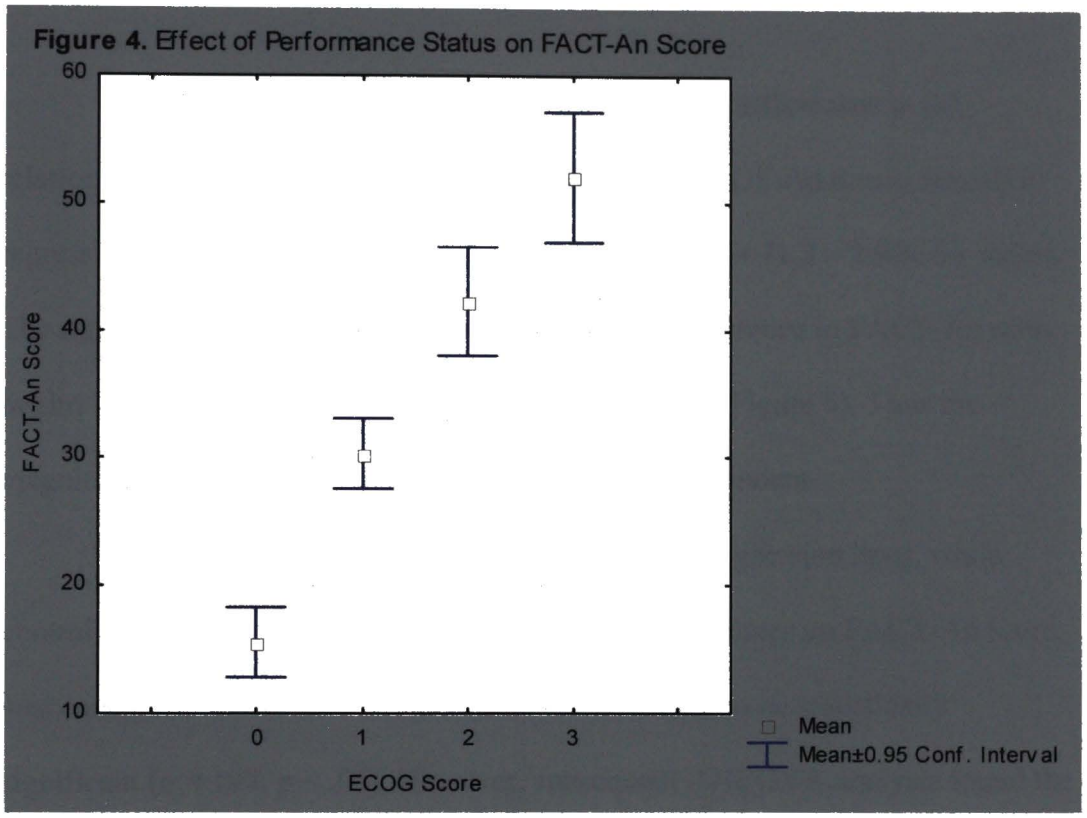
Patients receiving chemotherapy had significantly lower FACT-An scores by an independent samples t-test ($n = 197$, $p < .01$; Figure 3), and thus, current therapy was considered a covariate when determining gender difference. In addition, a one-way analysis of variance (ANOVA) revealed a significant mean difference in fatigue between patients of varying ECOG performance status scores ($n = 194$, $p < .001$; Figure 4). Subsequent regression analysis demonstrated that categorical increases in ECOG performance status were positively correlated with improved FACT-An scores ($n = 197$, $r = .6730$, $p < .001$).



Linear regression analysis of data from all patients with solid tumors revealed a non-significant, negative correlation between age and QOL as determined by the FACT-An subscale ($n = 197$, $r = -0.13$, $p = .0715$).



An independent samples t-test of data from all patients with solid tumors revealed a significant difference in the mean FACT-An score between those patients currently receiving chemotherapy and those who were not ($n = 197$, $p < .01$). Chemotherapy is associated with a greater patient perception of fatigue.

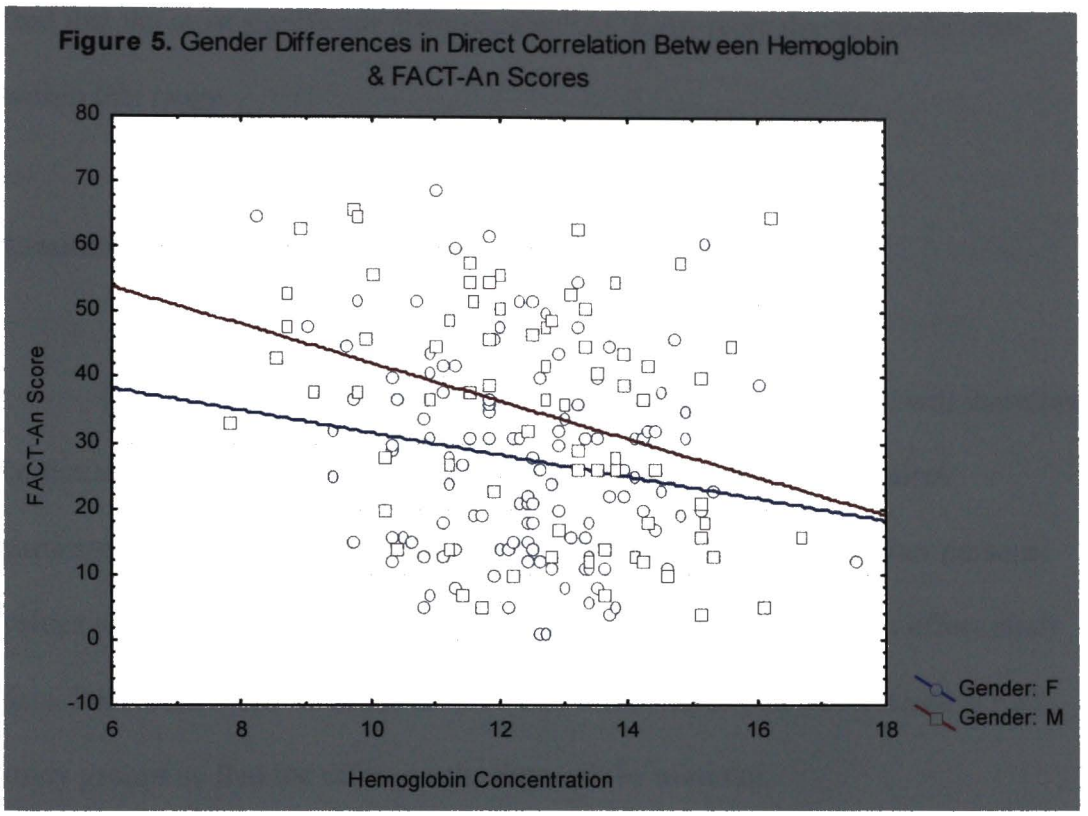


A one-way analysis of variance (ANOVA) of data from all patients with solid tumors revealed a significant mean difference in FACT-An subscale score between patients with ECOG performance scores 0 – 3 ($n = 194$, $p < .001$). The three patients who recorded a performance status of 4 were eliminated from this analysis due to their small numbers.

Relationship Between Gender & FACT-An Score

A simple regression analysis to compare gender differences in the relationship between hemoglobin concentration and FACT-An scores reveals a regression line of $y = 48.3 - 1.67x$ for females and of $y = 71.3 - 2.90x$ for males. The regression lines indicate that the gender-based difference in FACT-An score begins to diminish with increasing hemoglobin values (Figure 5). Thus the magnitude of this gender difference is hemoglobin-dependent.

An analysis of covariance to compare the two regression lines, while controlling the effects of the previously identified covariates on FACT-An score, was conducted across all hemoglobin levels and found to be statistically significant ($n = 197$, $p < .05$). However, subsequent ANCOVA analysis found the gender difference in FACT-An score to be significant when including only those patients within the 10.0 – 13.0 g/dL hemoglobin range ($n = 104$, $p < .01$). When patients with hemoglobin values of 13.0 g/dL and below were eliminated, ANCOVA did not reveal a statistically significant gender difference ($n = 75$, $p = 0.23$). In addition, gender difference in patients with values of less than 10.0 g/dL was also not found to be significant by ANCOVA analysis, but this may be due to the limited number of patients in this group ($n = 18$, $p = 0.35$). In a clinical setting, treatment of anemia generally begins at around 10.0 g/dL and terminates once hemoglobin concentration reaches 13 g/dL; therefore, it is not surprising to



Linear regression analysis of data from all patients with solid tumors calculated regression lines of $y = 48.3 - 1.67x$ for females and $y = 71.3 - 2.90x$ for males. Analysis of covariance for those patients with hemoglobin values within the 10.0 – 13.0 g/dL hemoglobin range revealed a significant difference in FACT-An scores between the two populations with male patients experiencing significantly greater fatigue ($n = 104$, $p < .01$).

find that the most significant difference in FACT-An score due to gender was within this range.

Limitations

Quality of life parameters are inherently subjective and there will therefore be limitations in any study which uses QOL outcomes or which requires participants to make subjective decisions. Cultural, religious, and other personal values will alter patient perception of QOL, and thus, will ultimately affect study data. Researchers are forced to assume that these biases will be balanced across study groups so that the effect on the data will be minimal.

Other non-subjective factors may play a role in patient QOL as well. Some researchers have claimed that control of tumor stage and progression, the effects of cancer therapy, and cancer therapy regimen must all be strictly controlled in order to collect valid data regarding the effect of epoetin therapy on QOL (24). However, *Demetri et al.* showed that there was an increase in QOL across all tumor types following epoetin treatment regardless of disease response to chemotherapy (13). Another study found that when using the FACT-G scale, neither age nor education level was significantly correlated with QOL (32). There are conflicting data on gender-based perceptions of QOL. A study of the QOL in rural cancer patients reported that women generally reported higher values; however, an analysis of 571 lung cancer patients found that females scored more

poorly on the EORTC QLQ C30 domain and symptom scales (32,11). Another study noted gender differences, but only in the affective, social, and power domains of QOL (34). In contrast, a study of cancer patients referred to home care, no gender differences were found in QOL, perceived emotional or physical health, performance status, or comorbidity (22). Furthermore, a study that measured psychological distress in cancer patient and their partners also found no QOL differences among male and female patients (22). As the actual role of gender in QOL outcomes is still unresolved, it is the best hope of this study that omitting the general QOL component and using only the anemia subscale will minimize subjectivity due to gender and any other variables.

Another limitation may be due to the voluntary nature of the study. There may be an inherent bias or common trait in all those willing to participate that may affect the validity of the study. For example, all patients who chose to participate may have a more positive view of their QOL than those who declined to participate. In addition, QOL data are difficult to collect from cancer patients as performance status declines (2). Patients with poorer performance statuses participated in lower numbers indicating that the data might not be truly representative of the patient population. Conversely, eliminating the patients who are bedridden over 50% of the time may be beneficial. Treatment of anemia would not be expected to have a significant effect on patients with severely deteriorating health; therefore, it would be difficult to determine the true relationship between QOL and hemoglobin levels in this population.

CHAPTER V

DISCUSSION

The correlation between QOL and anemia in patients with cancer is well established by a multitude of previous studies. This study was conducted to determine how this relationship is affected by patient gender.

Correlation analysis revealed a positive correlation between hemoglobin levels and QOL that, although relatively small, was consistent with data from several other trials (9). It has been postulated that this modest, yet statistically significant, correlation may be due to a possible nonlinear relationship between hemoglobin levels and QOL or interference from other uncontrolled confounders (9). During the course of cancer, a patient is subject to many conditions, due both to the underlying disease and therapy, which will diminish QOL. It is important to note that anemia is only one of these factors, and that, based on the findings of this study, it only explains approximately 5% of the variance in patient fatigue. Thus, comprehensive QOL management must include the management of multiple debilitating conditions beyond cancer-induced anemia.

The hemoglobin to QOL correlation was similar in magnitude to those found in studies which utilized the entire 47 – question FACT-An, as opposed to the 20 – question anemia subscale utilized in this trial. This finding suggests that the anemia subscale of the FACT-An may be used as a brief, independent

measure of fatigue. Physicians could potentially use the FACT-An subscale to evaluate patient fatigue in a significantly shorter period of time than is required by most QOL instruments. This could potentially bridge the gap between the number of physicians who recognize the importance of measuring patient QOL and those who actually do so in clinical practice.

Factors associated with poorer FACT-An scores were concurrent administration of chemotherapy, declining performance status, and male gender. The gender difference was found to be of greatest significance between 10.0 – 13.0 g/dL of hemoglobin. The age of the patients was not found to significantly affect level of fatigue.

According to ASCO guidelines, neither gender should receive rHuEPO for the treatment of anemia until the patient's hemoglobin concentration drops to 10.0 g/dL or below. At this point, a normal female would be expected to be at 63 – 83% of her baseline hemoglobin level (12 – 16 g/dL), while a male patient would be only at 56 – 71% of his baseline level (14 – 18 g/dL). Using the calculated regression lines for hemoglobin and FACT-An score, a female would be expected to have a FACT-An score near 31 out of a possible 80 at 10.0 g/dL. Conversely, a male patient would be expected to score about a 41 on the FACT-An subscale at this point. The male average FACT-An score does not reach the expected 31 points for the female score until a hemoglobin concentration near 13.5 g/dL is achieved. This discrepancy is most likely due to the variance in baseline

hemoglobin ranges between the genders which should be considered in anemia management.

The data collected from this study may be used to demonstrate the importance of using patient perceptions of QOL in today's clinical setting. Such data can aid the physician in making decisions about the efficacy of a particular treatment, as well as comparisons between treatments of similar efficacy. In this case, statistical analyses of these study data implicate a change, or, at the least, a more personalized approach to anemia management. Extensive data exist demonstrating that functional ability is optimized at a hemoglobin of 12 g/dL which is consistent with current ASCO guidelines. These studies have failed to account for gender as a possible confounder in the correlation of hemoglobin with QOL. The findings of this study indicate that at the 12 g/dL hemoglobin level men significantly greater fatigue than do female patients.

In conclusion, current ASCO guidelines for the management of anemia were developed when significant data for the role of epoetin therapy to improve patient QOL did not exist. The relationship between hemoglobin level and QOL has since been firmly established in many prospective studies that utilized rigorously validated patient questionnaires. Based on these results, new evidence-based guidelines should be adopted supporting the usage of epoetin therapy for QOL outcomes; however, it is important that these new guidelines take into account gender as a possible variable in the determination of patient QOL. To maximize patient functional abilities, these guidelines should support the

treatment of anemia on an individual basis. When this is not feasible, physicians should begin clinical interventions when anemic, male patients drop below a hemoglobin level of approximately 13.0 g/dL and should consider rHuEPO administration beyond traditional endpoints to ensure that male patients are not subject to greater fatigue than are their female counterparts throughout the course of anemia management.

APPENDIX

PATIENT QUESTIONNAIRE

Anemia Quality of Life Survey

To the patient:

You are being asked to participate in a research study. By completing the attached questionnaire, we will be able to measure your quality of life and the level of your physical activity to ensure that our care is meeting the needs of our patients. The results of this study may help us determine if every patient is receiving adequate supportive treatment from Texas Cancer Care. The questionnaire is a 21-question survey that should take no more than 5 minutes to complete. Participation in this study is completely voluntary; you are under no obligation to participate if you do not want to. The answers that you provide will be kept strictly confidential. Both the survey and your medical information will be coded by number and not by name. Your name will not be associated with any data. If at any point you have questions about this survey, you may contact Jennifer Crawford at (xxx) xxx-xxxx. Thank you for your time and participation.

Consent to Participate

Your signature below indicates that you have read the consent form and that you understand that your participation in this study is voluntary.

Name (Please Print)_____ Date_____

Signature_____

ECOG Performance Status

Please indicate by circling only one of the numbers below (0 – 4) which of the following statements best matches your level of activity over the last 7 days.

0.....I am fully active and able to participate in all activities without restriction.

1.....I am unable to perform physically strenuous activity, but I can perform light work (light house work or office work).

2.....I am able to care for myself completely, but I cannot carry out any work activities. I am up and about more than 50% of waking hours.

3.....I am capable of only limited self care. I am confined to a bed or chair more than 50% of waking hours.

4.....I cannot care for myself in any manner. I am always confined to a bed or chair.

Please turn to the next page and answer the following questions when you are finished.

FACT-An Subscale (Version 4)

By circling one (1) answer per line, please indicate how true each statement has been for you during the past 7 days.

	Not at all	A little bit	Some-what	Quite a bit	Very much
I feel fatigued	0	1	2	3	4
I feel weak all over	0	1	2	3	4
I feel listless ("washed out")	0	1	2	3	4
I feel tired	0	1	2	3	4
I have trouble starting things because I am tired	0	1	2	3	4
I have trouble finishing things because I am tired	0	1	2	3	4
I have energy	0	1	2	3	4
I have trouble walking	0	1	2	3	4
I am able to do my usual activities	0	1	2	3	4
I need to sleep during the day	0	1	2	3	4
I feel lightheaded (dizzy)	0	1	2	3	4
I get headaches	0	1	2	3	4
I have been short of breath	0	1	2	3	4
I have pain in my chest	0	1	2	3	4
I am too tired to eat	0	1	2	3	4
I am interested in sex	0	1	2	3	4
I am motivated to do my usual activities	0	1	2	3	4
I need help to do my usual activities	0	1	2	3	4
I am frustrated by not being able to do the things I want to do	0	1	2	3	4
I have to limit my social activity because I am tired	0	1	2	3	4

REFERENCES

1. Abels R. Erythropoietin for anaemia in cancer patients. *European Journal of Cancer.* 29 Suppl 2:S2-S8, 1993.

2. Bottomley A. The cancer patient and quality of life. *Oncologist. 7(2):120-5, 2002.*

3. Caro JJ, Salas M, Ward A, Goss G. Anemia as an independent prognostic factor for survival in patients with cancer: a systematic quantitative review. *Cancer.* 91: 2214-2221, 2001.

4. Cella D. Factors influencing quality of life in cancer patients: anemia and fatigue. *Seminars in Oncology.* 25(3 Suppl 7):43-6, 1998 Jun.

5. Cella D. The Functional Assessment of Cancer Therapy-Anemia (FACT-An) Scale: a new tool for the assessment of outcomes in cancer anemia and fatigue. *Seminars in Hematology.* 34(3 Suppl 2):13-9, 1997 Jul.

6. Cella, D. Tulsky, D. S. Gray G, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. *Journal of Clinical Oncology.* 11(3):570-9, 1993 Mar.

7. Cella D, Zagari MJ, Vandoros C, et al. Epoetin alfa treatment results in clinically significant improvements in quality of life in anemic cancer patients when referenced to the general population. *Journal of Clinical Oncology.* 21(2):366-73, 2003 Jan 15.

8. Cleeland CS, Demetri GD, Glaspy J, et al. Identifying hemoglobin level for optimal quality of life: results of an incremental analysis. *Proceeds of the American Society of Clinical Oncology.* 18:574a, 1999.

9. Crawford J, Cella D, Cleeland CS, et al. Relationship between changes in hemoglobin level and quality of life during chemotherapy in anemic cancer patients receiving epoetin alfa therapy. *Cancer.* 95(4):888-95, 2002 Aug 15.

10. Curt GA, Breitbart W, Cella D, et al. Impact of cancer-related fatigue on the lives of patients: new findings from the Fatigue Coalition. *Oncologist.* 5(5):353-60, 2000.

11. Dancey J, Zee B, Osoba D, et al. Gender and age influence baseline quality of life assessments in cancer patients. *European Journal of Cancer*. 33(8):S59, 1997.

12. Del Mastro L, Venturini M, Lionetto R, et al. Randomized phase III trial evaluating the role of erythropoietin in the prevention of chemotherapy-induced anemia. *Journal of Clinical Oncology*. 15(7):2715-21, 1997 Jul.

13. Demetri GD, Kris M, Wade J, et al. 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. *Journal of Clinical Oncology*. 16(10):3412-25, 1998 Oct.

14. Detmar SB, Aaronson NK. Quality of life assessment in daily clinical oncology practice: a feasibility study. *European Journal of Cancer*. 34:1181–1186, 1998.

15. Fried W, Barone-Varelas J. Regulation of the plasma erythropoietin level in hypoxic rats. *Experimental Hematology*. 12:706-711, 1984.

16. Glaspy J, Bukowski R, Steinberg D et al. Impact of therapy with epoetin alfa on clinical outcomes in patients with nonmyeloid malignancies during cancer chemotherapy in community oncology practice. *Journal of Clinical Oncology*. 15:1218-1234, 1997.

17. Gordon MS. Managing anemia in the cancer patient: old problems, future solutions. *Oncologist*. 7(4):331-41, 2002.

18. Gotay CC, Korn EL, McCabe MS, et al. Quality-of-life assessment in cancer treatment protocols: research issues in protocol development. *Journal of the National Cancer Institute*. 84:575–579, 1992.

19. Grant DG, Hussain A, Hurman D. Pre-treatment anemia alters outcome in early squamos cell carcinoma of the larynx treated by radical radiotherapy. *Journal of Laryngology & Otology*. 113:829-833, 1999.

20. Greimel ER, Padilla GV, Grant MM. Gender differences in outcomes among patients with cancer. *Psycho-Oncology*. 7(3):197-206, 1998 May-Jun.

21. Groopman JE, Itri LM. Chemotherapy-induced anemia in adults: incidence and treatment. *Journal of the National Cancer Institute*. 91:1616-1634, 1999.

22. Hagedoorn M, Buunk BP, Kuijer RG, et al. Couples dealing with cancer: role and gender differences regarding psychological distress and quality of life. *Psycho-Oncology*. 9(3):232-42, 2000 May-Jun.

23. Lee WR, Berkey B, Marcial V, et al. Anemia is associated with decreased survival and increased locoregional failure in patients with locally advanced head and neck carcinoma: a secondary analysis of RTOG 85-27. *International Journal of Radiation Oncology, Biology, Physics.* 42(5):1069-75, 1998 Dec 1.

24. Leidy NK, Revicki DA, Genteste B. Recommendations for evaluating the validity of quality of life claims for labeling and promotion. *Value in Health.* 2:113-27, 1999.

25. Ludwig H, Fritz E. Anemia in cancer patients. *Seminars in Oncology. 25:2-6, 1998.*

26. Mercadante S, Gebbia V, Marrazzo A, Filosto S. Anaemia in cancer: pathophysiology and treatment. *Cancer Treatment Reviews.* 26(4):303-11, 2000 Aug.

27. Morris J, Perez D, McNoe B. The use of quality of life data in clinical practice. *Quality of Life Research.* 7:85–91, 1998.

28. Osoba D. Lessons learned from measuring health-related quality of life in oncology. *Journal of Clinical Oncology.* 12:608–616, 1994.

29. Powers JS, Krantz SB, Collins JC, et al. Erythropoietin response to anemia as a function of age. *Journal of the American Geriatric Society.* 39(1):30-2, 1991.

30. Rizzo JD, Lichtin AE, Woolf SH, et al. American Society of Clinical Oncology. American Society of Hematology. Use of epoetin in patients with cancer: evidence-based clinical practice guidelines of the American Society of Clinical Oncology and the American Society of Hematology. *Journal of Clinical Oncology.* 20(19):4083-107, 2002 Oct 1.

31. Sabbatini P. The relationship between anemia and quality of life in cancer patients. *Oncologist.* 5 Suppl 2:19-23, 2000.

32. Schultz AA, Winstead-Fry P. Predictors of quality of life in rural patients with cancer. *Cancer Nursing.* 24(1):12-9, 2001 Feb.

33. Seidenfeld J, Piper M, Flamm C, et al. Epoetin treatment of anemia associated with cancer therapy: a systematic review and meta-analysis of controlled clinical trials. *Journal of the National Cancer Institute.* 93(16):1204-14, 2001 Aug 15.

34. Spiroch CR, Walsh D, Mazanec P, Nelson KA. Ask the patient: a semi-structured interview study of quality of life in advanced cancer. *American Journal of Hospice & Palliative Care.* 17(4):235-40, 2000 Jul-Aug.

35. Spivak JL. Anemia and erythropoiesis in cancer. *Advanced Studies in Medicine.* 2(17):612-619, 2002 Oct.

36. Spivak JL. The biology and clinical applications of recombinant erythropoietin. *Seminars in Oncology.* 25(3 Suppl 7):7-11, 1998 Jun.

37. Sweeney PJ, Nicolae D, Ignacio L, et al. Effect of subcutaneous recombinant human erythropoietin in cancer patients receiving radiotherapy: final report of a randomized, open-labelled, phase II trial. *British Journal of Cancer.* 77(11):1996-2002, 1998 Jun.

38. Tanaka T, Gotay CC. Physicians' and medical students' perspectives on patients' quality of life. *Academic Medicine.* 73:1003–1005, 1998.

39. Thatcher N, De Campos ES, Bell DR, et al. Epoetin alfa prevents anaemia and reduces transfusion requirements in patients undergoing primarily platinum-based chemotherapy for small cell lung cancer. *British Journal of Cancer.* 80:396-402, 1999.

40. Welch RS, James RD, Wilkinson PM, FB. Recombinant Human Erythropoietin and Platinum-Based Chemotherapy In Advanced Ovarian Cancer. *Cancer Journal from Scientific American.* 1(4):261, 1995 Nov.

41. WHOQOL Group. Study protocol for the World Health Organization project to develop a quality of life assessment instrument (WHOQOL). *Quality of Life Research.* 2:153–159, 1993.

42. Witthuhn BA, Quelle FW, Silvennoinen O et al. JAK2 associates with the erythropoietin receptor and is tyrosine phosphorylated and activated following stimulation with erythropoietin. *Cell.*74:227–236, 1993.

43. Yellen SB, Cella DF, Webster K, et al. Measuring fatigue and other anemia-related symptoms with the Functional Assessment of Cancer Therapy (FACT) measurement system. *Journal of Pain & Symptom Management.* 13(2):63-74, 1997 Feb.

44. Yoshimura A, Arai K. The Erythropoietin Receptor and Signal Transduction. *Oncologist.* 1(5):337-339, 1996.

45. Yoshimura A, Longmore G, Lodish HF. Point mutation in the exoplasmic domain of the erythropoietin receptor resulting in hormone-independent activation and tumorigenicity. *Nature*. 348:647–649, 1990.

46. Young T, Maher J. Collecting quality of life data in EORTC clinical trials—what happens in practice? *Psychooncology*. 8:260–263, 1999.

47. Anonymous. Double-blind, placebo-controlled study of the therapeutic use of recombinant human erythropoietin for anemia associated with chronic renal failure in predialysis patients. The US Recombinant Human Erythropoietin Predialysis Study Group. *American Journal of Kidney Diseases*. 18(1):50-9, 1991 Jul.