Variability of Patterns of Fatigue and Quality of Life Over Time Based on Different Breast Cancer Adjuvant Chemotherapy Regimens

Ann M. Berger, PhD, RN, AOCN®, FAAN, Kari Lockhart, MSN, APRN, and Sangeeta Agrawal, MSc

Purpose/Objectives: To examine the relationships among fatigue and physical and mental quality of life (QOL) and different adjuvant chemotherapy regimens in patients with stage I–IIIA breast cancer prior to, during, and after treatment.

Design: Longitudinal, descriptive design embedded in a randomized, clinical trial.

Setting: Outpatient oncology clinics in the midwestern United States.

Sample: 196 postoperative women, mean age of 52 years, receiving anthracycline-based chemotherapy regimens: dose-dense taxane, dose-standard taxane, or dose-standard without taxane.

Methods: The Piper Fatigue Scale and Medical Outcomes Study SF-36® (v.2) Survey were completed 48 hours prior to treatment 1, at treatments 4 and 8, and 30 days after the final treatment.

Main Research Variables: Fatigue, adjuvant chemotherapy regimen, and QOL.

Findings: Fatigue and mental QOL changed significantly over time for all regimens, but the patterns of change did not differ based on regimen. Physical QOL changed significantly over time for all regimens, and the pattern of change differed based on whether taxanes were received. Higher fatigue was correlated with lower physical and mental QOL prior to and 30 days after the final treatment, regardless of regimen.

Conclusions: Women who receive taxanes are at higher risk for lower physical QOL over time. Higher fatigue was associated with lower QOL regardless of the chemotherapy regimens.

Implications for Nursing: Clinicians should screen patients for fatigue and assess for contributing factors at clinic visits. Methods to integrate evidence-based fatigue interventions into practice should be tested and outcomes evaluated.

Breast cancer is the most frequently diagnosed cancer among women in the United States. According to the American Cancer Society ([ACS], 2009), an estimated 192,370 new cases of invasive breast cancer and an additional 62,280 new cases of in situ breast cancer are expected to occur in the United States in 2009. Since 1990, deaths from breast cancer in women younger than age 50 have decreased by 3.3% per year and, in women age 50 or older, by 2% per year (ACS, 2009). With a decrease in death rates has come an increase in five-year survival rates. The five-year survival rate is 98% for localized disease and 84% for regional breast cancer (ACS, 2009). This adds up to more than 2.3 million breast cancer survivors in the United States today (ACS, 2007).

Adjuvant chemotherapy usually is recommended after surgery for patients who are at significant risk for disseminated disease. Chemotherapy has been demonstrated to reduce the risk of breast cancer recurrence by 30%–50% (Moulder & Hortobagyi, 2008). Anthracycline-based regimens, including doxorubicin or epirubicin, are the breast cancer adjuvant chemotherapy standards of care (National Comprehensive Cancer Network [NCCN], 2008b). Medical oncologists perform a thorough workup to determine prognostic information to select one chemotherapy regimen over another. One of the newer laboratory tests that has been found to help determine which type of chemotherapy will be superior to another is the level of human epidermal growth factor receptor 2 (HER2-neu) expression (NCCN, 2008b). Lymph node status also helps oncologists decide whether to add taxanes (i.e., paxlitaxel or docetaxel) to the chemotherapy regimen (Box & Russel, 2004). Clinical trials have found improved disease-free and overall survival rates for lymph node-positive breast cancer by adding taxanes after standard anthracycline-based chemotherapy treatments and by delivery of identical doses of chemotherapy on a more frequent basis, referred to as dose-dense therapy (Moulder & Hortobagyi).

Cancer-related fatigue (CRF) is the most common complaint of patients (Prue, Rankin, Allen, Gracey, & Cramp, 2006). Fatigue has been reported by more than 90% of patients with cancer (Prue et al.). Factors that have been related to increased levels of CRF in patients include anxiety, depression, anemia, poor sleep quality, symptom distress, and lower levels of physical activity (de Jong, Courtens, Abu-Saad, & Schouten, 2002; Prue et al.). Evidence-based interventions for CRF have been rated for their effectiveness by the Oncology Nursing

Table 1. Demographic Characteristics of the Entire Sample at Study Entry

Characteristic	Dose-Dense Taxane (n = 75)	Dose-Standard Taxane (n = 46)	Dose Standard Without Taxane (n = 75)	Entire Sample[a] (N = 196)
Age (years)				
$\bar{X}$	51.8	51	53.5	52.3
SD	10.14	11.05	9.42	10.1
Range	29–83	32–74	30–79	29–83
Characteristic	**Dose-Dense Taxane (n = 75)**	**Dose-Standard Taxane (n = 46)**	**Dose Standard Without Taxane (n = 75)**	**Entire Sample[a] (N = 196)**
Ethnicity				
Hispanic	1	5	1	7
Non-Hispanic	74	41	74	189
Marital status				
Not partnered	23	9	21	53
Partnered	52	37	54	143
Education				
High school	21	7	19	47
Postsecondary education	54	39	56	149
Surgical procedure				
Lumpectomy	26	20	37	83
Modified mastectomy (MM)	23	11	20	54
MM with reconstruction	26	15	18	59
Cancer stage[b]				
I	5	8	48	60
II	50	32	24	107
IIIA	20	6	3	29

[a] Entire sample consists of participants with complete Piper Fatigue Scale and Medical Outcomes Study SF-36® (v.2) Survey data.

[b] $x^2(4) = 69.71$, $p < 0.01$

Society's Putting Evidence Into Practice (PEP) work (Mitchell, Beck, Hood, Moore, & Tanner, 2007) and by NCCN (2008a). Psychological and activity-based interventions have the strongest evidence and are recommended for clinical practice.

Adjuvant chemotherapy contributes to fatigue in women with breast cancer (Andrykowski, Schmidt, Salsman, Beacham, & Jacobsen, 2005). Women who received any type of adjuvant chemotherapy were more likely to develop CRF than patients who did not receive adjuvant chemotherapy (Andrykowski et al.; Woo, Dibble, Piper, Keating, & Weiss, 1998). Younger women who received adjuvant chemotherapy also reported more fatigue compared to older women, which may be a result of younger women receiving more aggressive chemotherapy regimens (de Jong et al., 2002). Research comparing fatigue in women receiving dose-dense to dose-standard adjuvant chemotherapy is limited. A pilot study (N = 15) by Sura, Murphy, and Gonzales (2006) found that those receiving dose-dense (14-day cycle) chemotherapy experienced significantly higher fatigue on day 3 of the first and second cycles than those who were on dose-standard (21-day cycle) chemotherapy regimens despite similar baseline fatigue. A randomized, open-label, four-arm phase II trial (N = 117) by Wildiers et al. (2009) agreed with Sura et al.'s findings. Those receiving dose-dense (10–14-day cycles) chemotherapy regimens experienced more severe fatigue (grade 3–4) compared to those receiving standard chemotherapy regimens.

Patients have reported that fatigue is the most common and distressing symptom experienced after completing chemotherapy (Andrykowski et al., 2005). Predictors of higher fatigue in patients with breast cancer after completing their initial chemotherapy treatment include depression, anxiety, pain, current tamoxifen use, and the type of surgical procedure (Haghighat, Akbari, Holakouei, Rahimi, & Montazeri, 2003). The strongest predictor of higher fatigue 30 days after the final taxane chemotherapy treatment was the fatigue level prior to receiving the initial chemotherapy treatment (Wielgus, Berger, & Hertzog, 2009). For many patients, increased levels of fatigue, physical and psychological issues, and poor sleep are associated with decreased QOL (Byar, Berger, Bakken, & Cetak, 2006).

QOL has been found to decline in almost all studies if the patient experienced more side effects than were expected or if moderate-to-severe fatigue occurred following the cancer treatments (Berger, Sankaranarayanan, & Watanabe-Galloway, 2007; Byar et al., 2006; Heidrich, Egan, Hengudomsub, & Randolph, 2006; Martin et al., 2006; Mills, Parker, Dimsdale, Robins-Sadler, & Ancoli-Israel, 2005). In a sample of 202 women who were an average of 23 months (range = 4–42 months) after a breast cancer diagnosis, younger women consistently rated their QOL lower than older women (Avis, Crawford, & Manuel, 2005). Women's (N = 1,047) physical and mental QOL decreased more with 21-day-cycle taxane-containing regimens (docetaxel, doxorubicin, and cyclophosphamide) than with 21-day-cycle nontaxane regimens (5-fluorouracil, doxorubicin, and cyclophosphamide), but returned to baseline at the 12-month follow-up visit (Martin et al., 2006). Chemotherapy regimens containing taxanes have been implicated as contributing to higher fatigue and lower QOL, but limited evidence is available regarding these relationships. A research gap exists on whether a significant difference is present in acute and late fatigue

Table 2. Chemotherapy Regimens for the Entire Sample at Study Entry

Regimen	Dose Standard (Every Three Weeks) (N = 119)	Dose Dense (Every Two Weeks) (N = 89)
Doxorubicin and cyclophosphamide for four cycles	73	17
Doxorubicin and cyclophosphamide for four cycles followed by taxane for four cycles	23	66
Doxorubicin and cyclophosphamide for four cycles followed by taxane weekly for 12 weeks	8	5
Doxorubicin, cyclophosphamide, and taxane	13	1
Doxorubicin and taxane for four cycles	1	–
Epirubicin and cyclophosphamide for eight cycles	1	–

Note. Taxane could be either docetaxel or paclitaxel.

and QOL among different chemotherapy regimens, specifically dose-dense taxane versus dose-standard taxane versus dose-standard without taxane. Therefore, this study's purpose was to examine relationships among fatigue, physical and mental QOL, and different adjuvant chemotherapy regimens in patients with stages I–IIIA breast cancer. Specific aims were addressed in participants receiving different chemotherapy regimens (dose-dense taxane versus dose-standard taxane versus dose-standard without taxane) prior to, at treatment 4, treatment 8, and 30 days after the final chemotherapy treatment. Specifically, the authors sought to

- Describe patterns and differences in fatigue over time.
- Describe patterns and differences in QOL (physical and mental) over time.
- Examine the relationships among fatigue, physical and mental QOL, and different chemotherapy regimens at each time.

Conceptual Framework

Piper's Integrated Fatigue Model (IFM) (Piper, Lindsey, & Dodd, 1987; Piper et al., 1998) provided the framework for this study. Six of the 14 dimensions of the IFM were examined to clarify the relationships between fatigue and the QOL dimensions represented by activity or exercise, disease, innate host factors, psychological, social, and treatment patterns.

Methods

Design

The study was a longitudinal, descriptive design, embedded in a randomized, control trial. The intervention group received a behavioral therapy intervention to improve sleep and decrease fatigue. The control group received information on healthy eating topics and general support (Berger et al., 2009).

Sample and Setting

From April 2003–May 2006, recruitment was conducted at two cancer centers and 10 community oncology clinics in the midwestern United States. Participants enrolled at least 48 hours prior to their first adjuvant chemotherapy treatment. Inclusion criteria were women aged 19 years and older, first diagnosis of stage I–IIIA breast cancer, post-modified radical mastectomy or lumpectomy, scheduled to begin four treatments of anthracycline-based IV chemotherapy with or without four doses of a taxane, and a Karnofsky Performance Scale score above 60. Exclusion criteria included a history of chronic insomnia; chronic fatigue syndrome; unstable heart, lung, or neuromuscular disease; insulin-dependent diabetes; sleep apnea; chronic steroid therapy; and night-shift employment.

Procedures

The primary site's institutional review board and 11 participating sites approved the study. A research nurse coordinator contacted potential participants in person or with their permission by telephone to provide study information and screen for eligibility. The screening form asked each participant to describe the intended plan of

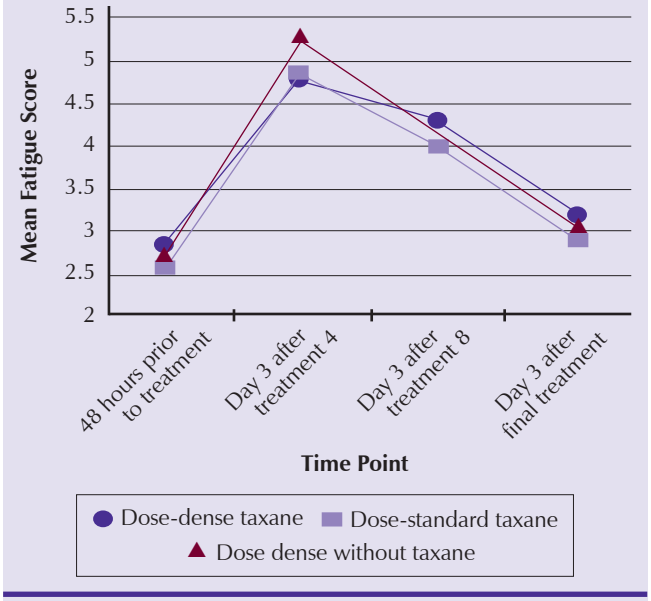

Figure 1. Patterns of Fatigue in Different Chemotherapy Regimens Over Time

Table 3. Piper Fatigue Scale Score at Selected Time Points

Variable	Chemotherapy Regimen: Dose-Dense Taxane	Dose-Standard Taxane	Dose Standard Without Taxane	All Cases
T0				
$\bar{X}$	2.86	2.56	2.61	2.7
SD	2.02	1.85	2.03	1.98
n	70	43	70	183
T4				
$\bar{X}$	4.88	4.93	5.28	5.05
SD	2.44	2.18	2.27	2.31
n	63	38	63	164
T8				
$\bar{X}$	4.33	3.97	–	4.23
SD	2.5	2.38	–	2.46
n	60	23	–	83
30 days				
$\bar{X}$	3.14	2.9	3.06	3.05
SD	2.28	2.15	2.18	2.2
n	65	40	64	169

T0—within 48 hours prior to treatment 1; T4—on day 3 after treatment 4; T8—on day 3 after treatment 8; 30 days—on day 1, 30 days after final treatment

chemotherapy treatments. If unsure, the research coordinator requested this information from the clinic staff. A research nurse visited interested and eligible women two or more days prior to their first treatment. After obtaining informed consent, participants were instructed on correct completion of research instruments on specific days before, during, and after each treatment. Additional details about the parent study are available (Berger et al., 2009).

Instruments

Measurements were completed prior to beginning treatment to determine that the randomization procedure was effective and that demographic, medical, or key variables were similar between groups.

The **Piper Fatigue Scale (PFS)**, a 22-item, four-dimension scale of subjective cancer-related fatigue, was used to measure multidimensional fatigue (Piper et al., 1998). Each item is anchored by two words and the participants indicate on a 10-point scale which word best describes their current fatigue. Fatigue can range from 0 (no fatigue) to 10 (a great deal of fatigue) and may be categorized as absent 0 (absent), 0.1–3.99 (mild), 4–6.99 (moderate), or 7–10 (severe). A mean score was calculated from the items. Content and concurrent validity of the PFS has been established in adults with cancer. The PFS took two to five minutes to complete two days prior to the first treatment, on the third day after treatments 4 and 8, and on day 1 of the 7-day measurement 30 days after the final treatment. Internal consistency reliability of the scale was 0.93–0.98 in this study.

The **Medical Outcomes Study SF-36® (v.2) Survey** was used to measure QOL (Ware, 2000). A recall measurement of status in all eight scales prior to diagnosis was completed at enrollment, and intermediate outcomes were evaluated at treatments 4 and 8 and 30 days after the final chemotherapy treatment. The physical QOL component score measures the patient's physical health status and the mental QOL component score measures the patient's mental health status. The alpha coefficients ranged from 0.68–0.94 at baseline and 0.83–0.94 at the 30-day measurement in this sample. Discriminate validity for this instrument has been established. Items are numerically scaled in a Likert format. It took 10–15 minutes to complete all eight scales.

Data Analysis

Data from 196 participants were double entered and inspected for artifacts, missing or out-of-range values, and normality. Once a participant was enrolled, the data were not excluded from any of the analyses to ensure

Table 4. Repeated Measures Mixed Model Analysis of Variance

Variable	Numerator df	Denominator df	F	p
Fatigue (Piper Fatigue Scale total score)				
• Main effect				
– Time[a]	3	143	67.79	< 0.01
Physical quality of life (SF-36® [v.2] physical and mental components)				
• Main effect				
– Time	3	123	7.64	< 0.01
– Chemotherapy regimen[b]	2	171	4.27	0.02
Mental quality of life (SF-36® [v.2] physical and mental components)				
• Main effect				
– Time	3	121	21.85	< 0.01

[a] Measurements taken within 48 hours prior to treatment 1, on day 3 after treatment 4, on day 3 after treatment 8, and on day 1, 30 days after last treatment.

[b] Dose-dense taxane, dose-standard taxane, or dose standard without taxane

Note. No effects by group (sleep intervention versus healthy eating control)

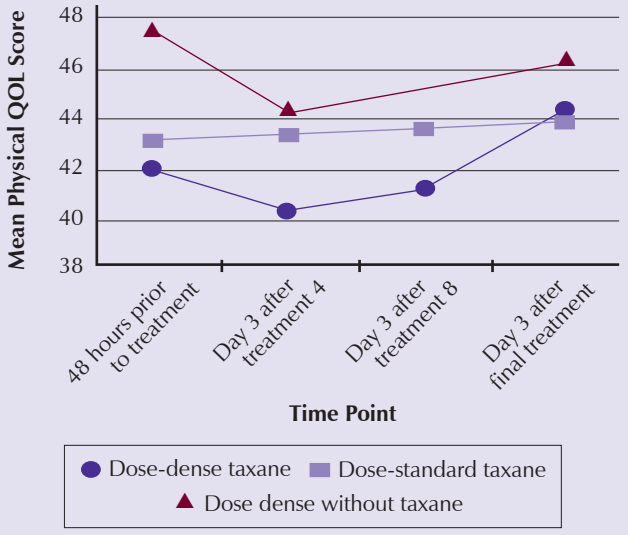

Figure 2. Patterns of Physical Quality of Life (QOL) in Different Chemotherapy Regimens Over Time

consistency with intent-to-treat analysis. Descriptive and inferential statistics were performed using SPSS® 15.0 statistical software. For all inferential tests, a significance level of $\alpha = 0.05$ (two-sided) was used. Demographics, medical characteristics, and study variables obtained prior to the first treatment were compared using t tests and chi-square tests between the groups to ensure comparability. Analyses included descriptives, RM-mixed model analysis of variances, and correlations.

Results

The majority of this study's participants were middle-aged, non-Hispanic, partnered women with postsecondary education (see Table 1). The sample was divided into three groups: patients who received dose-dense taxane regimens (n = 75), dose-standard taxane regimens (n = 46), and dose-standard without taxane regimens (n = 75). Participants who were prescribed a taxane-containing chemotherapy regimen (62%) received eight treatments; those who were not prescribed a taxane-containing regimen (38%) received four treatments. Almost 50% of the women received lumpectomies while the others received modified mastectomy with or without reconstruction. The chemotherapy regimens containing taxane therapy were more commonly prescribed in stages II and IIIA (see Table 2).

Patterns and Differences in Fatigue

Participants, no matter what chemotherapy regimen they received, reported fatigue that was initially mild, rose to moderate at treatments 4 and 8, and then dropped back down to mild 30 days after the final chemotherapy treatment (see Figure 1). Participants rated their fatigue highest at treatment 4. Fatigue levels for all regimens did not return to baseline levels by the 30-day measurement. Participants who received dose-dense taxane regimens consistently rated their fatigue higher, but not significantly higher, than those who received dose-standard taxane regimens and dose-standard without taxane regimens. The only exception was observed at treatment 4, when the participants who received dose-standard without taxane regimens rated their fatigue the highest overall (see Table 3). Fatigue changed significantly over time for all chemotherapy regimens ($F [3,143 = 67.79]$, $p < 0.001$) (see Table 4). Post-hoc analysis revealed that fatigue scores significantly changed between all time points measured ($p < 0.05$). No effects by group (sleep intervention versus healthy eating control) were found.

Patterns and Differences in Quality of Life

Physical quality of life: Participants, regardless of chemotherapy regimen, reported physical QOL scores that were initially slightly below the general population, dropped to lower levels at treatments 4 and 8, and then improved slightly 30 days after the final chemotherapy treatment (see Figure 2). Physical QOL changed significantly over time regardless of chemotherapy regimen ($F [3,123 = 7.64]$, $p < 0.001$) (see Table 4). Post-hoc analysis revealed that physical QOL scores significantly declined between baseline and treatments 4 and 8 and between treatments 4 and 8. Physical QOL scores returned to higher levels similar to those prior to treatment at 30 days after the final chemotherapy treatment.

Table 5. Physical Quality of Life (SF-36® [v.2] Physical Component Score) by Chemotherapy Regimen at Selected Time Points

Variable	Chemotherapy Regimen: Dose-Dense Taxane	Dose-Standard Taxane	Dose Standard Without Taxane	All Cases
T0				
$\bar{X}$	42.13	43.14	47.44	44.47
SD	10.31	9.35	8.99	9.84
n	65	40	69	174
T4				
$\bar{X}$	40.69	43.4	44.27	42.72
SD	8.93	11.28	8.81	9.58
n	57	37	59	153
T8				
$\bar{X}$	41.08	43.46	–	41.77
SD	9.4	10.17	–	9.62
n	54	22	–	76
30 days				
$\bar{X}$	44.54	44.14	46.74	45.13
SD	9.61	10.03	8.86	9.43
n	59	37	62	158

T0—within 48 hours prior to treatment 1; T4—on day 3 after treatment 4; T8—on day 3 after treatment 8; 30 days—on day 1, 30 days after final treatment

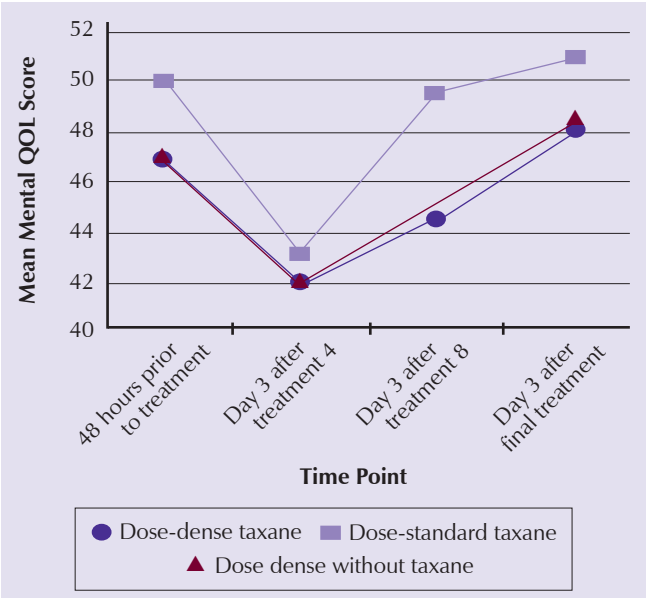

Figure 3. Patterns of Mental Quality of Life (QOL) in Different Chemotherapy Regimens Over Time

Participants who received dose-standard without taxane regimens reported significantly higher physical QOL than those who received taxane-containing regimens (F (2,171 = 4.27], $p = 0.02$) (see Tables 4 and 5). No effects by group (sleep intervention versus healthy eating control) were found.

Mental quality of life: Participants' mental QOL scores followed the same pattern regardless of the chemotherapy regimen (see Figure 3 and Table 6). Initially, mental QOL scores were similar to the general population's norms. All participants rated their mental QOL the lowest at treatment 4. Mental QOL scores began recovering at treatment 8 for participants who received taxanes, and participants rated their mental QOL the highest at the 30-day measurement. Participants who received dose-standard taxane regimens consistently rated their mental QOL higher than the rest of the participants, but results were not significantly different. The participants who received dose-dense taxane regimens rated their mental QOL the lowest at treatment 8. Mental QOL changed significantly over time regardless of chemotherapy regimen (F [3,121 = 21.85], $p < 0.001$). Post-hoc analysis revealed that mental QOL scores significantly changed between baseline and treatment 4, between treatments 4 and 8, and between treatment 4 and 30 days after the final chemotherapy treatment. A significant change also existed in mental QOL scores between the final taxane treatment (8) and 30 days later. No effects by group (sleep intervention versus healthy eating control) were found.

Relationships Among Fatigue, Quality of Life, and Chemotherapy Regimens

Pearson correlations between fatigue and the physical and mental QOL in different chemotherapy regimens revealed that prior to chemotherapy, the women who reported higher fatigue had lower physical and mental QOL ($r = -0.287$ to -0.661, $p < 0.05$–0.01). At treatment 4, women who received the dose-standard taxane regimens and the dose-standard without taxane regimens who reported higher fatigue also had lower physical and mental QOL ($r = -0.342$ to -0.722, $p = 0.01$). At treatment 8, women receiving dose-dense taxane and dose-standard taxane regimens who reported higher fatigue had lower physical and mental QOL ($r = -0.468$ to -0.722, $p = 0.01$). All women, regardless of regimen, who reported higher fatigue 30 days after the final chemotherapy treatment had lower physical and mental QOL ($r = -0.457$ to -0.646, $p = 0.01$) (see Table 7).

Discussion

This study addressed the question: Do patterns of fatigue and QOL differ over time based on breast cancer adjuvant chemotherapy regimens? Chemotherapy regimens examined included dose-dense taxane, dose-standard taxane, and dose-standard without taxane. Several important findings were made. First, fatigue changed significantly over time for all regimens, but the pattern of change did not differ based on regimen. Prior to beginning initial treatment, fatigue was mild but rose to moderate-to-severe intensity during the treatments and declined to mild intensity by the 30-day measurement. Second, physical QOL changed significantly over time for all regimens, and the pattern of change differed based

Table 6. Mental Quality of Life (SF-36® [v.2] Mental Component Score) by Chemotherapy Regimen at Selected Time Points

	Chemotherapy Regimen			
Variable	Dose-Dense Taxane	Dose-Standard Taxane	Dose Standard Without Taxane	All Cases
T0				
$\bar{X}$	47.01	50.08	47.21	47.8
SD	9.41	8.98	11.52	10.23
n	65	40	69	174
T4				
$\bar{X}$	41.73	42.91	41.81	42.05
SD	10.61	12.5	13.1	12.01
n	57	37	59	153
T8				
$\bar{X}$	44.84	49.29	–	46.13
SD	11.83	8.43	–	11.09
n	54	22	–	76
30 days				
$\bar{X}$	48.35	51.18	48.87	49.22
SD	10.33	10.1	11.07	10.57
n	59	37	62	158

T0—within 48 hours prior to treatment 1; T4—on day 3 after treatment 4; T8—on day 3 after treatment 8; 30 days—on day 1, 30 days after final treatment

Table 7. Correlations Between Total Fatigue (Piper Fatigue Scale Total Score) and Physical and Mental Components of Quality of Life (SF-36® [v.2]) in Selected Chemotherapy Regimens at Selected Time Points

	Domain			
	Physical		Mental	
Variable	r	n	r	n
T0				
Dose-dense taxane	–0.287*	64	–0.607**	64
Dose-standard taxane	–0.41**	40	–0.488**	40
Dose standard without taxane	–0.299*	69	–0.661**	69
T4				
Dose-dense taxane	–0.1	56	–0.189	56
Dose-standard taxane	–0.577**	36	–0.722**	36
Dose standard without taxane	–0.342**	59	–0.495**	59
T8				
Dose-dense taxane	–0.468**	54	–0.622**	54
Dose-standard taxane	–0.618**	22	–0.722**	22
Dose standard without taxane	–	–	–	–
30 days				
Dose-dense taxane	–0.476**	59	–0.52**	59
Dose-standard taxane	–0.601**	37	–0.646**	37
Dose standard without taxane	–0.457	62	–0.578**	62

* p = 0.05 level (two-tailed)

** p = 0.01 level (two-tailed)

T0—within 48 hours prior to treatment 1; T4—on day 3 after treatment 4; T8—on day 3 after treatment 8; 30 days—on day 1, 30 days after final treatment

on regimen. Women who received the dose-standard without taxane regimen had higher physical QOL over time compared to the women who received taxanes. Mental QOL changed significantly over time and the patterns of change were similar among all regimens. Regardless of the chemotherapy regimen, women who reported higher fatigue experienced lower physical and mental QOL prior to beginning chemotherapy and 30 days after the final treatment.

Dose-dense chemotherapy regimens have been implicated as contributing to higher fatigue, but this study did not support this belief. Findings regarding patterns of fatigue are consistent with the review of the literature. Fatigue has been documented as the most common and distressing symptom of women receiving any type of breast cancer adjuvant chemotherapy. Fatigue has been reported to increase from baseline with adjuvant chemotherapy, but gradually decline back to around baseline after the treatments are completed (Andrykowski et al., 2005; Avis et al., 2005; Banthia et al., 2006; Byar et al., 2006; de Jong et al., 2002; Heidrich et al., 2006; Prue et al., 2006). Because this study found no differences in fatigue between dose-dense and dose-standard regimens, other factors from the IFM (Piper et al., 1987) may have been more influential than treatment patterns in determining fatigue intensity.

The next important finding was that physical and mental QOL changed for participants in all regimens over time, and the highest physical and mental QOL scores were generally reported 30 days after the final chemotherapy treatment. A question this study tested and confirmed was that participants who received taxane-containing regimens reported significantly lower physical, but not mental, QOL than those who did not receive taxane-containing regimens. This finding may reflect less invasive surgery and better recovery prior to starting chemotherapy and lower toxicity from treatments. The findings are generally consistent with literature reporting the negative effect of adjuvant chemotherapy treatment on QOL and with the gradual improvement of QOL for most, but not all, after completing chemotherapy (Byar et al., 2006; Martin et al., 2006). This finding supports the results of a study (N = 1,047) conducted by Martin et al.

Another important finding was that women who reported higher fatigue had lower physical and mental QOL prior to, during, and after adjuvant chemotherapy treatments. This finding is consistent with the literature (Andrykowski et al., 2005; Avis et al., 2005; Banthia et al., 2006; Byar et al., 2006; de Jong et al., 2002; Heidrich et al., 2006; Mills et al., 2005; Prue et al., 2006).

This study had strengths and limitations. Strengths included a large sample, reliable and valid instruments, and longitudinal design. Limitations were that the subjective instruments for fatigue and QOL might not have been sensitive enough to detect the changes that may have been captured through one-on-one interviews or other qualitative approaches. Another limitation is that the written tools were used to measure fluctuating symptoms and the timing of tool completion could not be tightly controlled. The lack of true baseline values for fatigue and QOL and the lack racial or ethnic diversity among participants also were limitations to the study.

Implications for Practice and Research

Clinicians should screen for fatigue according to NCCN guidelines (NCCN, 2008a). The authors recommend screening using a visual analog scale (VAS) at each clinical visit. When patients rate their fatigue intensity as four or higher, clinicians should assess for factors contributing to fatigue to determine appropriate interventions (NCCN, 2008a). Early identification of individuals who report higher fatigue and lower physical and mental QOL is needed to prevent negative outcomes. Initiating an intervention that is acceptable to the patient who reports higher fatigue early in the course of treatment may reduce fatigue and prevent lower QOL during treatment and in survivors. Healthcare providers should reassess

fatigue and determine its impact on physical and mental QOL. Effective management of common side effects of adjuvant chemotherapy and referrals for more intense symptom management can assist in relieving fatigue and its negative impact on QOL. All patients, particularly those presenting with lower physical health status prior to treatment or those prescribed taxane-containing regimens, should be taught that exercise (Mitchell et al., 2007) and activity enhancement (NCCN, 2008a) are highly recommended to reduce fatigue and promote physical QOL. An individualized exercise plan is suggested.

Implications for research involve measurement and future analysis. Many definitions and tools exist to measure fatigue and QOL. Commonly used VAS scales do not account for the multidimensional concepts of fatigue and QOL. Future research should establish reliable and valid tools for patients with cancer that are useful to clinicians and researchers. The M.D. Anderson Symptom Inventory (Cleeland et al., 2000) is one tool that meets this criterion. Qualitative research can explore patients' experiences and meanings of fatigue and decreased QOL. Use of advanced statistical prediction models of higher fatigue and lower QOL also are recommended.

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Ann M. Berger, PhD, RN, AOCN®, FAAN, is a professor and Dorothy Hodges Olson Endowed Chair in Nursing, and Advanced Practice Nurse director, PhD program, Kari Lockhart, MSN, APRN, is an adult acute care oncology nurse practitioner, and Sangeeta Agrawal, MSc, is a research analyst, all in the College of Nursing at the University of Nebraska Medical Center in Omaha. This research was funded by grants awarded to Berger from the National Institutes of Health and the National Institute of Nursing Research (#5R01NR007762-05). Berger can be reached at aberger@unmc.edu, with copy to editor at ONFEditor@ons.org. (Submitted June 2008. Accepted for publication September 5, 2008.)

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References

American Cancer Society. (2007). *Cancer facts and figures 2007.* Retrieved September 22, 2007, from http://www.cancer.org/downloads/STT/CAFF2007PWSecured.pdf

American Cancer Society. (2009). *Cancer facts and figures 2009.* Retrieved July 27, 2009, from http://www.cancer.org/downloads/STT/500809web.pdf

Andrykowski, M.A., Schmidt, J.E., Salsman, J.M., Beacham, A.O., & Jacobsen, P.B. (2005). Use of a case definition approach to identify cancer-related fatigue in women undergoing adjuvant therapy for breast cancer. *Journal of Clinical Oncology, 23*(27), 6613–6622.

Avis, N.E., Crawford, S., & Manuel, J. (2005). QOL among younger women with breast cancer. *Journal of Clinical Oncology, 23*(15), 3322–3330.

Banthia, R., Malcarne, V.L., Roesch, S.C., Ko, C.M., Greenbergs, H.L., Varni, J.W., et al. (2006). Correspondence between fatigue reports in breast cancer survivors. *Journal of Behavioral Medicine, 29*(3), 269–279.

Berger, A.M., Kuhn, B.R., Farr, L.A., Lynch, J.C., Agrawal, S., Chamberlain, J., et al. (2009). Behavioral therapy intervention trial to improve sleep quality and cancer-related fatigue. *Psycho-Oncology, 18*(6), 634–646.

Berger, A.M., Sankaranarayanan, J., & Watanabe-Galloway, S. (2007). Current methodological approaches to the study of sleep disturbances and QOL in adults with cancer. *Psycho-Oncology, 16*(5), 401–420.

Box, B.A., & Russell, C.A. (2004). Breast cancer. In D.A. Casciato (Ed.), *Manual of clinical oncology* (5th ed., pp. 233–253). Philadelphia: Lippincott Williams and Wilkins.

Byar, K.L., Berger, A.M., Bakken, S.L., & Cetak, M.A. (2006). Impact of adjuvant breast cancer chemotherapy on fatigue, other symptoms, and quality of life [Online exclusive]. *Oncology Nursing Forum, 33*(1), E18–E26. Retrieved July 20, 2009, from http://ons.metapress.com/content/um1281005428t806/fulltext.pdf

Cleeland, C.S., Mendoza, T.R., Wang, X.S., Chou, C., Harle, M.T., Morrissey, M., et al. (2000). Assessing symptom distress in cancer patients: The M.D. Anderson Symptom Inventory. *Cancer, 7*(89), 1634–1646.

de Jong, N., Courtens, A.M., Abu-Saad, H.H., & Schouten, H.C. (2002). Fatigue in patients with breast cancer receiving adjuvant chemotherapy. *Cancer Nursing, 25*(4), 283–297.

Haghighat, S., Akbari, M.E., Holakouei, K., Rahimi, A., & Montazeri, A. (2003). Factors predicting fatigue in breast cancer patients. *Supportive Care in Cancer, 11*(8), 533–538.

Heidrich, S.M., Egan, J.J., Hengudomsub, P., & Randolph, S.M. (2006). Symptoms, symptom beliefs, and quality of life of older breast cancer survivors. *Oncology Nursing Forum, 33*(2), 315–322.

Martin, M., Lluch, A., Segui, M.A., Ruiz, A., Ramos, M., Adrover, E., et al. (2006). Toxicity and health-related quality of life in breast cancer patients receiving adjuvant docetaxel, doxorubicin, cyclophosphamide (TAC) or 5-fluorouracil, doxorubicin, and cyclophosphamide (FAC): Impact of adding primary prophylactic granulocyte-colony stimulating factor to the TAC regimen. *Annals of Oncology, 17*(8), 1205–1212.

Mills, P.J., Parker, B., Dimsdale, J.E., Robins-Sadler, G.R., & Ancoli-Israel, S. (2005). The relationship between fatigue and quality of life and inflammation during anthracycline-based chemotherapy in breast cancer. *Biological Psychology, 69*(1), 85–96.

Mitchell, S.A., Beck, S.L., Hood, L.E., Moore, K., & Tanner, E.R. (2007). Putting evidence into practice: Evidence-based interventions for fatigue during and following cancer and its treatment. *Clinical Journal of Oncology Nursing, 11*(1), 99–113.

Moulder, S., & Hortobagyi, G.N. (2008). Advances in the treatment of breast cancer. *Clinical Pharmacology and Therapeutics, 83*(1), 26–36.

National Comprehensive Cancer Network. (2008a). *NCCN Clinical Practice Guidelines in Oncology™: Cancer-related fatigue* [v.1.08]. Retrieved February 23, 2008, from http://www.nccn.org/professionals/physician_gls/PDF/fatigue.pdf

National Comprehensive Cancer Network. (2008b). *NCCN Clinical Practice Guidelines in Oncology™: Invasive breast cancer* [v.1.08]. Retrieved September 4, 2008, from http://www.nccn.org/professionals/physician_gls/PDF/breast.pdf

Piper, B.F., Dibble, S.L., Dodd, M.J., Weiss, M.C., Slaughter, R.E., & Paul, S.M. (1998). The Revised Piper Fatigue Scale: Psychometric evaluation in women with breast cancer. *Oncology Nursing Forum, 25*(4), 677–684.

Piper, B.F., Lindsey, A.M., & Dodd, M.J. (1987). Fatigue mechanisms in cancer patients. *Oncology Nursing Forum, 14*(6), 17–23.

Prue, G., Rankin, J., Allen, J., Gracey, J., & Cramp, F. (2006). Cancer-related fatigue: A critical appraisal. *European Journal of Cancer, 42*(7), 846–863.

Sura, W., Murphy, S.O., & Gonzales, I. (2006). Level of fatigue in women receiving dose-dense versus standard chemotherapy for breast cancer: A pilot study. *Oncology Nursing Forum, 33*(5), 1015–1021.

Ware, J.E. (2000). SF-36 Health Survey. *Spine, 25*(24), 3130–3139.

Wielgus, K.K., Berger, A.M., & Hertzog, M. (2009). Predictors of fatigue 30 days after completing anthracycline plus taxane adjuvant chemotherapy. *Oncology Nursing Forum, 36*(1), 38–48.

Wildiers, H., Dirix, L., Neven, P., Prove, A., Clement, P., Squifflet, P., et al. (2009). Delivery of adjuvant sequential dose-dense FEC-Doc to patients with breast cancer is feasible, but dose reductions and toxicity are dependent on treatment. *Breast Cancer Treatment Research, 114*(1), 103–112.

Woo, B., Dibble, S.L., Piper, B.F., Keating, S.B., & Weiss, M.C. (1998). Differences in fatigue by treatment methods in women with breast cancer. *Oncology Nursing Forum, 25*(5), 915–920.