Fatigue and Physical Activity in Patients Undergoing Hematopoietic Stem Cell Transplant

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Purpose/Objectives: To examine the patterns of fatigue, physical activity, health status, and quality of life before and after high-dose chemotherapy and hematopoietic stem cell transplantation (HSCT) and to examine the feasibility of obtaining real-time fatigue and physical activity data.

Design: Prospective, repeated measures.

Setting: Two midwestern academic medical centers.

Sample: Convenience sample of autologous or allogeneic patients undergoing HSCT (N = 20 baseline, N = 17 post-transplant).

Methods: Subjects were assessed over a five-day period before and after HSCT for a total of 10 days. Subjects rated fatigue intensity three times daily and wore a wrist actigraph to measure physical activity. At the end of both five-day periods, subjects completed measures of perceived health status (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30) and life satisfaction (Quality of Life Index).

Main Research Variables: Fatigue, physical activity, perceived health status, and quality of life.

Findings: Study results indicate that fatigue significantly increased and physical activity decreased following high-dose chemotherapy and HSCT. The decline coincided with diminished physical, emotional, role, and cognitive functioning. The symptoms that patients experienced (i.e., fatigue, pain, nausea and vomiting, sleep disturbances, appetite loss, and diarrhea) increased during the acute post-transplant period. No significant changes in life satisfaction were found.

Conclusions: The study findings suggest that patients receiving high-dose chemotherapy followed by HSCT experience increased fatigue, reduced physical activity, diminished functioning, and poorer quality of life immediately after transplant. Findings demonstrate that real-time fatigue and physical activity data can feasibly be collected in acutely ill patients.

Implications for Nursing: Patients undergoing HSCT require considerable supportive nursing care immediately following transplant. Clinicians and researchers need to strive for effective symptom management to improve the likelihood of successful outcomes.

Key Points . . .

- ➤ Patients experience increased fatigue and decreased physical activity following the preparatory regimen and hematopoietic stem cell transplantation (HSCT).
- ➤ Patients report diminished functioning and increased symptomatology following HSCT, although no changes in life satisfaction were reported.
- ➤ Real-time fatigue and physical activity data can feasibly be collected from patients who undergo intensive cancer therapies.

Intensive cancer therapy, such as high-dose chemotherapy followed by hematopoietic stem cell transplantation (HSCT), has the potential to affect all aspects of patients' lives, particularly during the immediate post-transplant period. Very little is known about the patterns of fatigue, physical activity, health status, and quality of life (QOL) during this period. Problems such as fatigue and decreased physical activity may result in long-term functional consequences, eventually affecting patients' ability to maintain or return to productive roles in society. Obtaining subjective data during the acute post-transplant period is difficult because patients frequently are too ill to complete long questionnaires or participate in lengthy interviews. Likewise, obtaining objective

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data regarding physical activity during the same time period is difficult because patients may be too fatigued to participate in tests of physical performance. No studies found in the stem cell transplant literature examined the relationship between fatigue and physical activity and its subsequent impact on health status and QOL. This information is needed to provide a better understanding of the problems experienced by patients so that effective interventions can be planned to mitigate them. The information also can be used to identify patients who are at greater risk, so that interventions can be initiated as early as possible to increase the likelihood of successful outcomes. The purpose of the current study was to examine the patterns of fatigue, physical activity, health status, and QOL before and after high-dose chemotherapy and HSCT. A secondary purpose was to determine the feasibility of using the Actiwatch-Score® (Mini Mitter Company, Inc., Bend, OR), a wrist actigraph with a subjective event marker, as a patient-tolerable means for obtaining real-time fatigue and physical activity data pretransplant and during the acute post-transplant period.

Relevant Literature

Cancer-related fatigue has been described as one of the most prevalent and debilitating side effects associated with cancer and its treatment. This insidious phenomenon has been defined in numerous ways, including a lack of energy, tiredness, malaise, insomnolence, exhaustion, an inability to concentrate, and a lack of motivation (Aistars, 1987; Holley, 2000; Portenoy & Itri, 1999; Winningham et al., 1994). Fatigue may occur as a result of physical activity reduction, the disease process, cancer treatment, or a broad range of physical, psychological, and situational factors (Winningham et al.). The Fatigue Guidelines Panel of the National Comprehensive Cancer Network (2005) defined *cancer-related fatigue* as "an unusual, persistent, subjective sense of tiredness related to cancer or cancer treatment that interferes with usual functioning" (p. MS-2). The definition is particularly useful for clinical studies, in that it recognizes the subjective nature of fatigue and delineates the phenomenon from an individual's response to fatigue (e.g., interference with usual functioning).

High-dose chemotherapy followed by HSCT is one example of an intensive treatment that has the potential to cause significant debilitating fatigue. Although the prevalence and severity of fatigue following chemotherapy, radiation therapy, and multimodality treatment have been well documented, relatively little is known about the incidence and severity of fatigue during the immediate post-HSCT period. In the studies that have examined fatigue in patients undergoing HSCT, the symptom has been described as intense, with some cancer survivors reporting complications for years following treatment (Gruber, Fegg, Buchmann, Kolb, & Hiddemann, 2003; Jacobsen & Stein, 1999; Knobel et al., 2000; Macquart-Moulin et al., 2000; Molassiotis & Morris, 1999; Winer et al., 1999; Zittoun, Achard, & Ruszniewski, 1999).

Several studies examined fatigue immediately following HSCT. In one longitudinal study, patients with breast cancer undergoing autologous HSCT (n = 31) reported significantly more fatigue immediately following a marrow ablative regimen than did a group of matched healthy controls (n = 49) (Hann et al., 1999). Fatigue was significantly related to increased time to engraftment, longer hospitalization, and increased psychosocial distress, suggesting that patients who experience greater fatigue also undergo a more difficult treatment course. In another study investigating high-dose sequential chemotherapy with repeated stem cell support, 96% of patients with inflammatory breast cancer (N = 79) reported fatigue during the third cycle of intensive chemotherapy, with 62% reporting fatigue lasting longer than one week and 73% reporting fatigue that was quite or very distressing (Macquart-Moulin et al., 2000). A third longitudinal study examined changes in fatigue immediately following HSCT (Hacker & Ferrans, 2003). Although statistically significant differences in fatigue over time were not found, clinically important changes were identified. Fatigue initially increased immediately prior to hospital discharge, but some improvement was noted two and six weeks following discharge.

The previously noted studies provide preliminary information regarding patterns of fatigue. However, information still is needed regarding the incidence, severity, and associated factors following HSCT. Studies of other patients with cancer have shown that higher levels of fatigue have been associated with a reduction in physical activity (Berger, 1998; Berger & Higginbotham, 2000; Sarna & Conde, 2001), a decrease in functional ability (Irvine, Vincent, Graydon, Bubela, & Thompson, 1994), and, ultimately, lower QOL (Lovely, Miaskowski, & Dodd, 1999).

Physical inactivity may result during and following a lengthy hospitalization. The deleterious effects of prolonged bed rest and sustained inactivity have been well documented. Potential cardiopulmonary effects include orthostatic intolerance or postural hypotension (Illman, Stiller, & Williams, 2000); thromboembolism, even in patients with chemotherapy-induced thrombocytopenia (Barbui, Finazzi, Grassi, & Marchioli, 1996), pneumonia (Beck-Sague, Banerjee, & Jarvis, 1993); and left ventricular atrophy (Katsume et al., 1992; Maron, Pelliccia, Spataro, & Granata, 1993). Prolonged immobility affects the musculoskeletal system, leading to loss of muscle mass (Ferrando, Stuart, Brunder, & Hillman, 1995); loss of muscle strength, particularly in the lower weight-bearing extremities (Suzuki et al., 1994); increased risk of muscle injury along with slower recovery times (Prou & Marini, 1997); and increased risk of joint contractures and exacerbation of osteoporosis (Nishimura et al., 1994). The negative effects of immobility on mood status also have been documented (Ishizaki et al., 1997). Some of the effects occurred in as little as seven days of bed rest, with most occurring after 14–20 days. Because of prolonged hospitalization and the risk of complications, patients undergoing HSCT may be at risk for similar complications, especially if physical activity is severely limited while hospitalized.

No studies found in the stem cell literature examined changes in physical activity during the immediate post-transplant period. This may be partially the result of methodologic difficulties associated with quantifying objective measures of physical activity in patients undergoing HSCT. Clinical observations, however, suggest that patients undergoing HSCT experience significant decreases in physical activity following transplant. Information regarding physical activity immediately following HSCT is needed because the toxic effects of the preparatory regimen and prolonged hospitalization may lead to a marked reduction in physical activity, with resultant consequences.

Several researchers have used wrist actigraphy as a means of quantifying physical activity in patients with cancer. In

these studies, increased physical activity as measured by wrist actigraphy was associated with decreased fatigue (Sarna & Conde, 2001). In patients with breast cancer, the patterns of fatigue, rest, and physical activity varied during adjuvant therapy, with fatigue and physical activity exhibiting a roller-coaster pattern (Berger, 1998). Patients reported more fatigue during treatment and less fatigue at cycle midpoints. Increases in fatigue were consistently associated with decreased physical activity and occasionally associated with rest indicators. No studies were found in the literature that used wrist actigraphy as a means of quantifying physical activity in patients undergoing HSCT. Use of noninvasive means for assessing physical activity may provide a mechanism for capturing much-needed information.

Conceptual Framework

Wilson and Cleary's (1995) Conceptual Model of Patient Outcomes was used to guide the current study. The model proposes the dominant, causal relationships among traditional, biologic, and physiologic variables to health-related QOL. In the model, five types of health outcomes are proposed: (a) biologic and physiologic variables, (b) symptoms, (c) functional status, (d) general health perceptions, and (e) QOL. In the current study, Wilson and Cleary's model guided the description of symptoms, functional ability, health perceptions, and overall QOL.

Methods

Design

This descriptive, exploratory study used a prospective, repeated-measures design to assess changes in fatigue, physical activity, health status perceptions, and QOL in patients undergoing HSCT. Subjects were assessed for five days before and after high-dose chemotherapy and HSCT, for a total of 10 days. Baseline data were collected prior to hospital admission for the transplant (time 1) and from day 4–8 following the transplant (time 2). Data from time 1 were used as baseline information. Data from time 2 were expected to coincide with the period of profound neutropenia and the impact of acute side effects from the intensive therapy. Data from time 2 were used to evaluate the types of complications experienced following intensive therapy and stem cell rescue, as well as the ability and willingness of patients to provide complete information with wrist actigraphy when experiencing the full impact of intensive therapy.

Sample and Setting

Adult patients electing to undergo HSCT at two midwestern academic medical centers were invited to participate. The patient accrual period lasted nine months, until a convenience sample of 20 participants was obtained. All participants met the eligibility criteria that specified an age of 18 years or older at the time of transplantation, the ability to speak English, cognitive ability to comprehend the study, and no current psychiatric diagnosis. Two patients declined to participate, stating that they felt too ill. Several patients meeting the eligibility criteria were not invited to participate because of a lack of time for collecting five days of data between the initial patient identification and admission to the hospital for transplant. All study participants were outpatients during the pretransplant data collection phase and inpatients during the post-transplant data collection phase.

Instruments

Fatigue: Fatigue was measured with two scales. The Actiwatch-Score contains a subjective event marker on the face of the activity monitor. The subjective event marker was programmed to be used as a single-item, global, self-report scale to measure real-time fatigue intensity. The fatigue intensity scores ranged from 1 (no fatigue) to 10 (worst fatigue). Data entered into the subjective event marker were stored in the onboard memory of the device.

The second fatigue scale used was the fatigue subscale of the **European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30 (EORTC QLQ-C30)** (Aaronson et al., 1993). The fatigue subscale of the EORTC QLQ-C30 consists of three items that measure physical fatigue using a four-point Likert scale. In a review of seven published studies, Aaronson, Cull, Kaasa, and Sprangers (1996) reported adequate to high internal consistency for the fatigue scale (range = 0.80–0.91). Moderate to high correlations (r = 0.67, 0.72, 0.75) of the fatigue subscale of the EORTC QLQ-C30 with the physical fatigue subscale of the Fatigue Questionnaire in patients with advanced cancer and cancer survivors provided support for convergent validity (Knobel et al., 2003).

Physical activity: The Actiwatch-Score was used to quantify physical activity. The accelerometer uses a piezoelectric sensor to monitor the occurrence and degree of motion. A motion sensor integrates the degree and speed of motion to produce an electrical current that varies in magnitude so that an increase in the degree of motion and speed produces an increase in voltage. The information is stored as activity counts in the onboard Actiwatch-Score memory. The device is sensitive to motion in all directions.

The Actiwatch-Score consists of an activity monitor and a disposable wristband and is compact, lightweight, water resistant, and battery operated. The device is placed on a subject's nondominant hand. Levels of activity may be recorded for as many as 22 days when the Actiwatch-Score epoch monitoring is set to one-minute intervals. In terms of size, the Actiwatch-Score resembles a small wristwatch. Successful use of wrist actigraphy to quantify physical activity and sleep disturbances has been reported in several studies involving patients with cancer (Berger, 1998; Berger & Higginbotham, 2000; Miaskowski & Lee, 1999; Sarna & Conde, 2001) and critically ill patients (Grap, Borchers, Munro, Elswick, & Sessler, 2005).

Health status perceptions: The EORTC QLQ-C30 version 3.0 is a 30-item tool consisting of five functional scales (physical, role, emotional, cognitive, and social), a global QOL or health status scale, three multi-item symptom scales (fatigue, pain, and nausea and vomiting), and a number of single-item questions concerning dyspnea, appetite loss, sleep disturbance, constipation, diarrhea, and financial impact (Aaronson et al., 1996). The EORTC QLQ-C30 primarily measures patients' perceptions of health status in terms of deviations from an optimal state of functioning. For example, questions such as "during the past week, have you felt weak?" are answered with responses ranging from 1 (not at all) to 4 (very much). The four-point Likert scale is used for 28 items. The global QOL or health status scale uses a seven-point Likert scale, with choices ranging from 1 (very poor) to 7 (excellent). Questions

on the multi-item subscales are averaged and then converted to a scale with a range of 0–100. A profile of subscale scores is obtained. Higher scores on the five functional scales and the global QOL or health status scale represent a higher level of functioning. Higher scores on the symptom scales and the single-item questions indicate a higher degree of symptomatology and thus poorer QOL. The EORTC QLQ-C30 is a well-established instrument, and the psychometric properties have been reported previously (Aaronson et al., 1993, 1996; Bjordal & Kaasa, 1992; Hacker, 2003; Osoba, Aaronson, Zee, Sprangers, & te Velde, 1997; Osoba et al., 1994).

In the current study, Cronbach's alpha coefficients were computed for all multi-item subscales. Adequate reliability (alpha coefficient ≥ 0.65) was established for most of the subscales (physical functioning = 0.68, role functioning = 0.82, emotional functioning = 0.87, cognitive functioning = 0.72, global QOL or health status = 0.88, fatigue = 0.82, pain = 0.78, and nausea and vomiting = 0.65). The social functioning subscale did not demonstrate adequate reliability (Cronbach's alpha = 0.49). The means and standard deviations of the subscale are reported for comparison purposes only, and their meaning must be interpreted with caution.

Quality of life: The **Quality of Life Index (QLI)** was used to measure life satisfaction (Ferrans, 1990; Ferrans & Powers, 1985). The QLI is a well-established tool that has been used in a variety of populations, including patients with cancer, bone marrow transplant recipients, and patients undergoing HSCT (Belec, 1992; Ferrans; Hacker & Ferrans, 2003). The QLI produces an overall QOL score and subscale scores relative to four specific domains: (a) health and functioning, (b) social and economic, (c) psychological or spiritual, and (d) family. The two-part, 70-item instrument measures satisfaction with various aspects of life (part 1) as well as the relative importance of each specific aspect to the individual (part 2). For instance, "how satisfied are you with your health?" in part 1 corresponds with "how important to you is your health?" in part 2. The possible responses for part 1 range from 1 (very dissatisfied) to 6 (very satisfied). Likewise, the responses for part 2 range from 1 (very unimportant) to 6 (very important). The satisfaction responses are weighted by the related importance responses, producing a more accurate reflection of QOL. Possible scores range from 0–30. Higher scores indicate greater satisfaction with life. The reliability and validity of the QLI have been well established (Anderson & Ferrans, 1997; Bliley & Ferrans, 1993; Cowan, Young-Graham, & Cochrane, 1992; Ferrans; Ferrans & Powers, 1985, 1992; Hughes, 1993; Kim & Rew, 1994; R.B. King, 1996; Papadantonaki, Stotts, & Paul, 1994; Stuifbergen, 1995).

In the present study, Cronbach's alpha coefficients were computed for the total QLI and multi-item subscales. Adequate reliability was established for the total QLI (Cronbach's alpha = 0.87) and health and functioning, social and economic, and psychological or spiritual subscales (Cronbach's alphas = 0.77, 0.71, and 0.77, respectively). The family subscale did not demonstrate adequate reliability (Cronbach's alpha = 0.18). The means and standard deviations for the subscale are reported for comparison purposes only, and their meaning must be interpreted with caution.

Data Collection Schedule and Procedures

The study received institutional review board approval from two academic medical centers. Eligible patients were invited to participate during a scheduled visit to the hospital's clinic before hospitalization for high-dose chemotherapy and HSCT. At that time, the study's objectives were explained, written informed consent was obtained, and a short demographic form was completed. Wrist actigraphs were placed on patients' nondominant hands. Patients were instructed to leave the wrist actigraph in place for the next five days, until the principal investigator or research assistant removed it. During the five days, patients rated the intensity of fatigue on a 1 (no fatigue) to 10 (worst fatigue) scale three times each day (10 am, 2 pm, and 6 pm). Patients were instructed to enter the rating directly into the wrist actigraph via the subjective event marker on the face of the device. An alarm on the wrist actigraph sounded at the specified times to remind patients to complete the data. Because of the expected variability in time associated with

Table 1. Demographic Characteristics

Characteristic	n	%
Gender		
Male	9	45
Female	11	55
Race		
White or Caucasian (not Latino or Hispanic)	7	35
Black or African American (not Latino or Hispanic)	8	40
Latino, Hispanic, or Mexican American	3	15
Native American or American Indian	–	–
Asian or Pacific Islander	1	5
Other	1	5
Marital status		
Never married	2	10
Married	12	60
Divorced	5	25
Separated	1	5
Educational level		
Some high school or less	4	20
Graduated from high school	4	20
Some college or more	12	60
Annual income ($)		
Less than 20,000	4	20
21,000–40,000	7	35
41,000–60,000	6	30
More than 61,000	3	15
Source of insurance		
Public aid	5	25
Medicare	4	20
Health maintenance organization	3	15
Preferred provider organization	6	30
Other	2	10
Diagnosis (N = 17)		
Lymphoma	4	23
Chronic myelogenous leukemia	1	6
Acute myelogenous leukemia	3	18
Acute lymphocytic leukemia	1	6
Multiple myeloma	5	29
Myelofibrosis	2	12
Plasma cell leukemia	1	6
Type of transplant (N = 17)		
Autologous	10	59
Allogeneic	7	41
Source of allogeneic cells (N = 7)		
Matched sibling	3	43
Matched unrelated donor	4	57

N = 20 unless otherwise indicated

placing and removing the wrist actigraph, only 72 hours of complete, continuous data from 8 am on day 2 through 8 am on day 5 were used for data analysis. Patients were instructed to carry on with normal activities, including bathing and showering, because the Actiwatch-Score is water resistant. On day 5, the wrist actigraph was removed, and patients completed the EORTC QLQ-C30 and QLI, which were administered by the principal investigator or research assistant. Subjects received a copy of the questionnaire to view while answering the questions to facilitate the interview process. The interview took approximately 15–30 minutes to complete. The procedures for collecting data at time 2 were the same as those described for time 1. The wrist actigraph was placed on the nondominant hand of subjects on the fourth day following the transplant and removed on the eighth day. The EORTC QLQ-C30 and QLI were administered on day 8.

Data Analysis

Data analyses were performed using SPSS® (SPSS Inc., Chicago, IL). Descriptive statistics were calculated for all study variables. Internal consistency estimates (Cronbach's alpha) were assessed for all multi-item Likert scales. Paired-sample t tests and one-way repeated-measures analysis of variance were used to determine changes in fatigue, physical activity, health status, and QOL before and after HSCT (alpha level = 0.05, two tailed). No data were missing for the EORTC QLQ C-30 and QLI. Missing data for the real-time fatigue assessment were not replaced.

Results

Sample

The mean age of the sample was 48.65 years (range = 23–64 years). Table 1 summarizes the descriptive statistics for the demographic variables. Twenty patients were enrolled in the study and completed baseline research activities. Three patients did not receive HSCT because of medical complications. Seventeen patients participated in real-time research activities following the transplant (time 2), and 15 subjects completed time 2 questionnaires. Two of the 17 subjects were too ill to complete the time 2 questionnaires. The response rates for the various measures are listed in Table 2.

Fatigue

Real-time fatigue assessment: Response rates were calculated before and after transplant. Response rates were considered acceptable if subjects completed seven of the nine real-time fatigue assessments (i.e., on three consecutive days at 10 am, 2 pm, and 6 pm). Twenty subjects participated in real-time fatigue assessment before transplantation. Fifty percent (n = 10) of the subjects entered fatigue intensity ratings across all data collection points. An additional 35% (n = 7) of the subjects entered fatigue intensity ratings across eight of the nine data collection points. Three subjects were missing data from three or more data collection points. As a result, the overall response rate before transplant was 85%.

Seventeen subjects participated in the real-time fatigue assessment following transplant. Fifty-three percent (n = 9) of the subjects entered fatigue intensity ratings across all data collection points. Twelve percent (n = 2) responded eight out of nine times, and an additional 12% (n = 2) responded seven out of nine times. The overall response rate following transplant was 77% (n = 13). Four patients were missing data from three or more data collection points, but two were hospitalized in an intensive care unit because of deteriorating health status and one was experiencing intermittent periods of confusion.

Fatigue intensity ratings were classified as mild (1–3), moderate (4–6), or severe (7–10), based on National Comprehensive Cancer Network recommendations (Mock et al., 2000). Only subjects who completed two of the three daily assessments were included in the analysis. The majority of patients rated their fatigue intensity as mild prior to transplant (day 1 = 75%, day 2 = 83%, day 3 = 88%) (see Figure 1). Following the transplant, most patients rated their fatigue intensity as moderate to severe (day 5 = 90%, day 6 = 77%, and day 7 = 80%) (see Figure 2).

Fatigue subscale of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30: The means and standard deviations for the fatigue subscale of the EORTC QLQ-C30 are presented in Table 3. Significant differences in fatigue were found before and after transplant ($p < 0.001$), with patients reporting significantly higher levels of fatigue following transplant. In addition, the EORTC QLQ-C30 mean scores for the fatigue

Table 2. Response Rates for Study Measures

Measure	Time 1 Response Rate (N = 20)	Time 2 Response Rate (N = 17)	Comments
Fatigue (one-item fatigue intensity rating scale)	Range = 17–20	Range = 14–17	For times 1 and 2, subjects were included in the daily rating of fatigue if two of three assessments in the day were completed.
Fatigue (EORTC QLQ-C30 subscale)	20	15	At time 2, two subjects were too ill to complete the questionnaire eight days following the transplant.
Physical activity (accelerometer)	20	17	At time 2, three subjects did not receive the transplant.
Health status (EORTC QLQ-C30)	20	15	At time 2, two subjects were too ill to complete the questionnaire eight days following the transplant.
Quality of life (QLI)	20	15	At time 2, two subjects were too ill to complete the questionnaire eight days following the transplant.

EORTC QLQ-C30—European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30; QLI—Quality of Life Index

Note. Twenty subjects initially enrolled. Seventeen subjects received a stem cell transplant. The three remaining subjects did not receive a transplant during the study period.

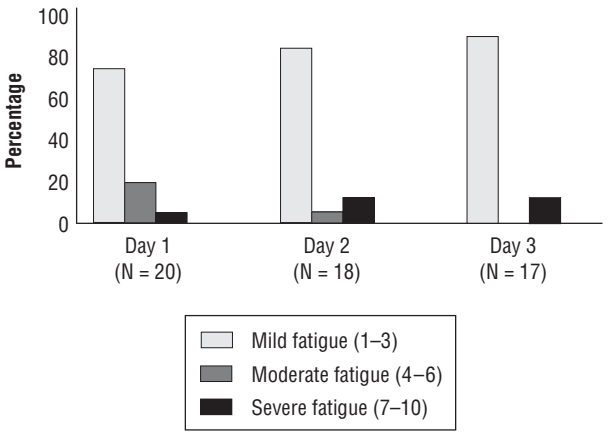


Figure 1. Fatigue Intensity Ratings Prior to Transplantation

subscale were evaluated for clinically important changes over time. The changes are based on previously published criteria for interpreting EORTC QLQ-C30 scores (M.T. King, 1996; Osoba, Rodrigues, Myles, Zee, & Pater, 1998). Clinically important changes in mean scores are classified as small (mean score change of 5–10), moderate (mean score change of 11–20), or large (mean score change of more than 20). A mean score change of 41.48 in the fatigue subscale indicates a large clinically important difference before and after transplantation.

Physical Activity

The means and standard deviations for daily physical activity counts (three consecutive 24-hour periods) before and after transplantation are presented in Table 4. Significant differences in physical activity were found before and after transplantation ($p < 0.001$), with a 58% reduction in physical activity following the transplant (see Figure 3). The physical activity levels were not significantly different among the three consecutive days of physical activity before the transplant. Likewise, no significant differences existed among the three consecutive days of physical activity after the transplant. An example of one patient's actigram (one 24-hour period before and after transplant) is presented in Figure 4. A visual examination of the pattern of physical activity suggests changes before and after HSCT as well. Before transplant, patients generally experienced more defined periods of physical activity and inactivity. Following transplant, the amount of physical activity over the course of 24 hours appeared to stay the same, with less clearly defined periods of physical activity versus inactivity. The trend occurred in most subjects.

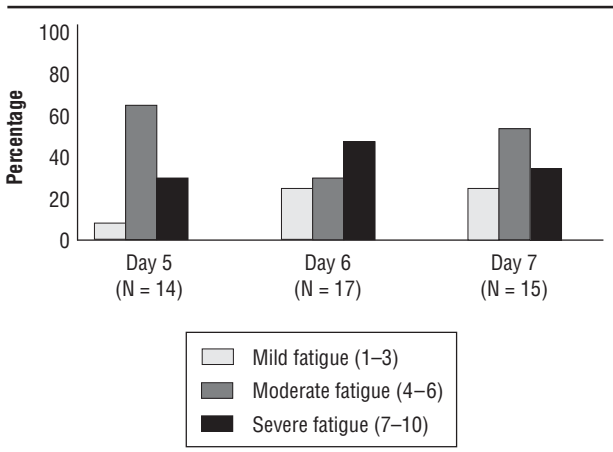


Figure 2. Fatigue Intensity Ratings Post-Transplantation

Health Status Perceptions

Mean scores and standard deviations for the EORTC QLQ-C30 are presented in Table 3. Paired-sample t tests resulted in the following significant differences before and after HSCT: all functional subscales (physical, $p < 0.05$; role, $p < 0.01$; emotional, $p < 0.05$; and cognitive, $p < 0.05$), global QOL or health status ($p < 0.05$), all multi-item symptom subscales (fatigue, $p < 0.001$; pain, $p < 0.001$; and nausea or vomiting, $p < 0.001$), and three single-item symptom questions (appetite loss, $p < 0.001$; sleep disturbance, $p < 0.01$; and diarrhea, $p < 0.001$). Figure 5 depicts the mean score changes for the functional subscales. Figures 6 and 7 depict the mean score changes for the multi-item symptom subscales and single-item symptom questions, respectively. Patients reported significant declines in physical, role, emotional, and cognitive functioning in the immediate post-transplant period. The decline in functioning coincided with significant increases in symptomatology. Patients reported increased fatigue, pain, nausea and vomiting, appetite loss, sleep disturbance, and diarrhea in the immediate post-transplant period. Global QOL or health status was significantly worse ($p < 0.05$) post-transplant.

The EORTC QLQ-C30 mean scores for the multi-item subscales were evaluated for clinically important changes over time. As previously stated, the changes are based on

Table 3. Mean Scale and Item Scores of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30

Subscale or Single-Item Question	Time 1		Time 2	
	$\bar{X}$	SD	$\bar{X}$	SD
Functional scales				
Cognitive	88.89	14.99	73.34	25.82
Emotional	86.11	18.00	70.56	24.17
Physical	79.11	19.33	54.22	27.93
Role	73.33	33.81	36.67	40.43
Social	78.89	22.24	56.67	30.73
Global quality of life	38.89	12.47	31.67	12.28
Symptom scales				
Fatigue	29.63	22.48	71.11	31.09
Pain	23.33	28.03	66.67	38.32
Nausea and vomiting	6.67	13.80	68.89	26.63
Single items				
Appetite loss	17.78	30.51	86.67	27.60
Constipation	6.67	13.80	17.78	27.79
Diarrhea	8.89	19.79	51.11	33.01
Dyspnea	15.56	27.79	22.22	32.53
Financial impact	31.11	32.04	40.00	40.24
Sleep disturbances	20.00	32.85	48.89	39.57

N = 15

Table 4. Physical Activity Counts for 72 Consecutive Hours

	Hours 0–24		Hours 25–48		Hours 49–72	
Time	$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD
1	202.55	127.33	178.58	65.60	181.82	98.16
2	70.82	30.03	75.29	32.54	89.53	49.66

N = 17

Note. Time 1 was defined as the period prior to high-dose chemotherapy and stem cell transplantation, and time 2 was the period after transplantation (days 5–7).

published criteria for interpreting EORTC QLQ-C30 scores (M.T. King, 1996; Osoba et al., 1998). Examining the magnitude of mean score changes revealed clinically important differences in physical functioning, emotional functioning, cognitive functioning, role functioning, fatigue, pain, and nausea or vomiting. The clinically important differences ranged from moderate to large in magnitude, with symptoms (fatigue, pain, nausea and vomiting) showing the largest change before and after transplantation.

Quality of Life

The mean scores and standard deviations for the total QLI and four subscales are presented in Table 5. No statistically significant differences were found for total QLI or the health and functioning, social and economic, and psychological or spiritual subscales. A difference of two points or more in the total score or subscale score has been identified as a clinically important change (Bliley & Ferrans, 1993; Hathaway et al., 1994; Johnson, Wicks, Milstead, Hartwig, & Hathaway, 1998). In the present study, a decline of 3.68 points on the health and functioning subscale suggested a clinically important difference in terms of dissatisfaction with health and functioning, although statistical significance was not found.

Discussion

Research in cancer symptoms, whether disease or treatment related, was identified as a scientific priority in the 2004 Oncology Nursing Society Research Survey (Berger et al., 2005).

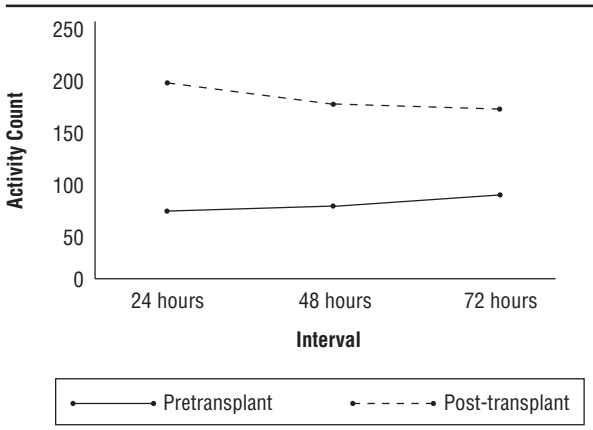


Figure 3. Changes in Daily Physical Activity Counts

Patients receiving intensive therapies, such as HSCT, may be at higher risk for developing multiple concurrent cancer symptoms and side effects from therapy. The cancer symptoms and side effects may further influence physical activity, perceived health status, and QOL. The ability to collect data on the variables during the period of profound neutropenia and during the impact of acute side effects from dose-intensive therapy was of particular interest in the current study. In addition, the patients undergoing HSCT experienced significantly increased fatigue, reduced physical activity, diminished functioning, increased symptomatology, and poorer QOL during the acute post-transplant period. The findings demonstrated that real-time fatigue and physical activity data, as well as perceived health status and QOL data, can be collected feasibly when patients are experiencing the full burden of their dose-intensive therapy (i.e., so long as the subject burden is reasonable). This study was intentionally designed to keep subject burden at a minimal level.

This study is the first to report real-time fatigue data in patients with cancer receiving intensive therapy. A computerized ecologic momentary assessment approach for collecting fatigue data (computerized real-time collection of data) was chosen to avoid problems with recall inaccuracies and allow for improved documentation of compliance (Stone, Shiffman, Schwartz, Broderick, & Hufford, 2002). Documentation of compliance is particularly important when attempting to capture data from patients who are acutely ill and may not be able to accurately recall their cancer symptoms. A 1–10 fatigue intensity rating scale was chosen because of the ease of use in acutely ill patients and its ability to capture repeated measurements of fatigue throughout the day without placing undue burden on participants. Although numeric intensity ratings do not provide information regarding the multidimensional nature of fatigue, this type of scale is suggested for use as a fatigue-screening device in clinical situations (Glaus, 1993; Mock, 2001). Furthermore, numeric intensity ratings are more likely to be implemented in clinical practice, thus facilitating understanding of research findings by clinicians and the translation of research findings into clinical practice.

As expected, patients undergoing HSCT experienced significant fatigue in the acute post-transplant period. Patients reported changes in fatigue using the numeric fatigue intensity rating scale and the fatigue subscale of the EORTC QLQ-C30, strengthening the study findings. The majority of patients rated their fatigue as mild prior to transplantation and moderate or severe afterward with the 1–10 scale. A significant difference also was found in the fatigue subscale of the EORTC QLQ-C30 when comparing pretransplant to post-transplant scores.

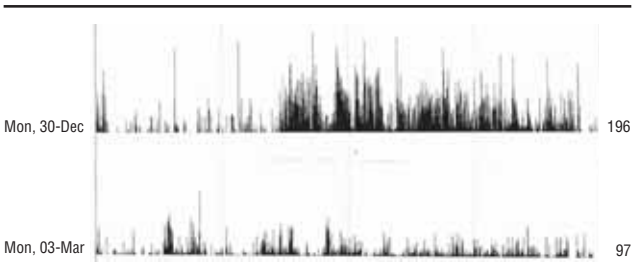
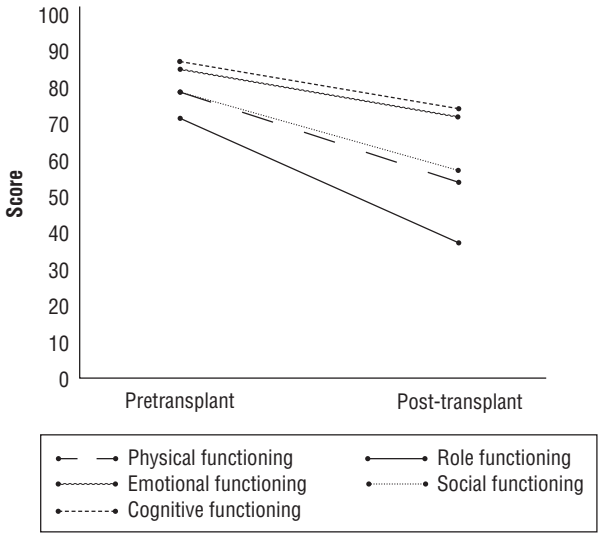


Figure 4. Actigraph Example for One Patient Before and After Transplantation



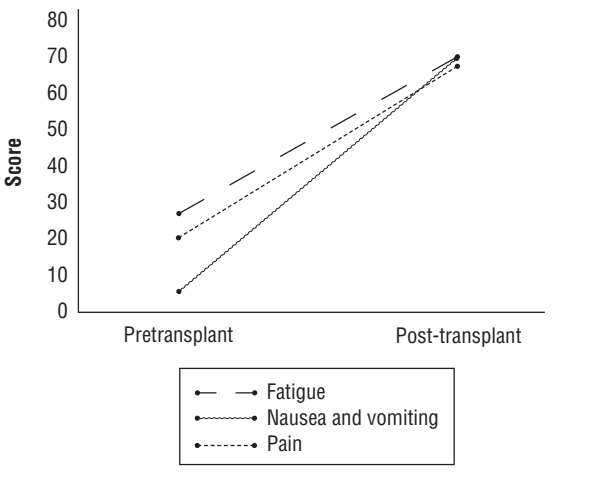
Note. Higher scores indicate a higher level of functioning.

Figure 5. Changes in Functional Scales of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30

The mean score change of 41.48 indicates a large, clinically important change, providing further evidence that the fatigue experienced by patients undergoing HSCT is considerably more intense immediately following the transplant.

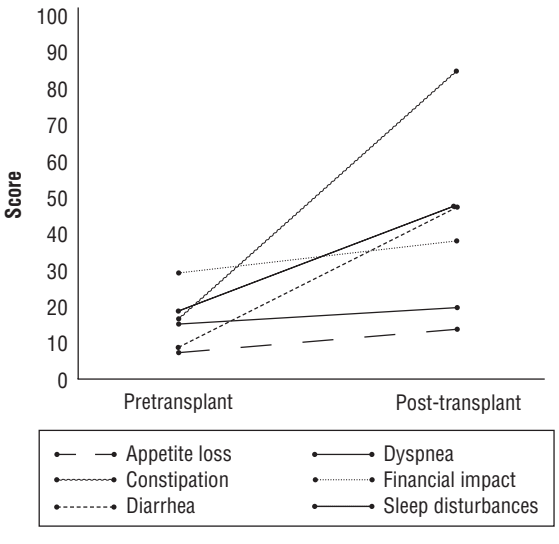
The study findings suggesting significant differences in fatigue before and immediately after transplantation are supported by a longitudinal study that examined fatigue in patients undergoing autologous HSCT (El-Banna et al., 2004). In that study, El-Banna et al. used the Piper Fatigue Scale, a multidimensional, self-report fatigue instrument. Fatigue was measured over multiple time points prior to and immediately after high-dose chemotherapy and autologous HSCT. Patients reported significantly increased fatigue from baseline (prior to chemotherapy) to day 7 following the transplant for total fatigue and all dimensions of fatigue, except the cognitive or mood subscale. How does El-Banna et al.'s study relate to the current study? The similar data collection points in both studies, heterogeneity of samples (current study: autologous and allogeneic transplant recipients; El-Banna et al.'s study: autologous transplant recipients only), and multiple measures of fatigue (current study: real-time fatigue assessment using a numeric intensity rating scale and fatigue subscale of the EORTC QLQ-C30; El-Banna et al.'s study: Piper Fatigue Scale) provide further support for the fatigue findings and enhance the generalizability of the findings from both studies. Fatigue experienced by patients undergoing HSCT significantly increases in the immediate post-transplant period. Interventions that reduce or alleviate fatigue in patients undergoing HSCT are needed. The current study's investigators currently are working on developing an intervention to address this problem.

One limitation of the current study was its inability to use or collect fatigue data in some patients following transplant. Selection bias may be present in favor of the patients who were physically able to complete the self-report study measures following transplant. Four of the 17 patients were missing at least three real-time fatigue ratings following the transplant, and two patients were unable to complete the fatigue subscale of the EORTC QLQ-C30 on day 8 post-transplant. Two of the patients were very seriously ill and transferred to a medical intensive care unit, and another was experiencing intermittent periods of confusion. Although the three patients did not complete all measures of fatigue post-transplant, they likely would not have been able to provide any type of self-report data under the circumstances. Furthermore, for the two patients transferred to the medical intensive care unit, given their medical condition, their fatigue ratings may have been



Note. Higher scores indicate a higher degree of symptomatology.

Figure 6. Changes in Multi-Item Symptom Scales of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30



Note. Higher scores indicate a higher degree of symptomatology.

Figure 7. Changes in Single-Item Questions of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30

Table 5. Mean Overall and Subscale Scores of the Quality of Life Index

	Time 1		Time 2	
Scale	$\bar{X}$	SD	$\bar{X}$	SD
Overall quality of life	23.08	3.20	21.95	5.62
Health and functioning	21.04	4.48	17.40	6.79
Social and economic	22.54	4.49	25.14	6.14
Psychological or spiritual	24.47	3.38	22.27	7.95
Family	27.18	2.64	27.74	3.39

N = 15

higher and not lower than the other participants' ratings. If the two patients' scores had been included, the fatigue scores may have been even higher.

This study is the first to provide real-time physical activity data using wrist actigraphy in patients undergoing HSCT. As expected, patients experienced significant declines in physical activity while hospitalized following the transplant, which is consistent with clinical observations. The amount of decline in physical activity, a 58% reduction, was surprising. For patients who often require lengthy hospitalizations (e.g., patients undergoing HSCT), the prolonged physical inactivity may result in serious complications and hamper recovery from the dose-intensive therapy and HSCT. Methods to increase or maintain previous levels of physical activity following transplantation are needed.

The relationship between reduction in physical activity and cancer-related fatigue in patients undergoing HSCT requires further exploration. Although the exact cause for physical inactivity following HSCT is unknown, reductions in activity levels may be associated with cancer-related fatigue in this population. Whether a reduction in physical activity leads to increased fatigue or whether increased fatigue following dose-intensive therapy leads to a reduction in physical activity is not known. In either case, prolonged physical inactivity and accompanying fatigue may lead to considerable loss of muscle mass and decreased strength, especially if the symptoms last longer than 7–14 days. Furthermore, patients undergoing HSCT with persistent fatigue may have difficulty resuming physical activity and regaining strength, even as the toxic effects of high-dose chemotherapy subside. Eventually, physical inactivity, reduced strength, and fatigue lead to decreased capacity for normal activity, which may result in long-term functional consequences that affect patients' ability to maintain or return to productive roles in society. Although the current study did not address these questions, they certainly are relevant areas for research.

A number of statistically significant changes were found on the functional, global QOL, and symptom subscales of the EORTC QLQ-C30 as well as on several single-item symptom questions. The study findings suggest that patients experience diminished capacity to function and significant toxicity in the acute post-transplant period. Patients reported significant declines in physical, role, emotional, and cognitive functioning following transplant. The changes in functional ability coincided with significant increases in cancer symptoms, including fatigue, pain, nausea and vomiting, appetite loss, sleep disturbances, and diarrhea. Although the changes were expected and consistent with the literature (Bellm, Epstein, Rose-Ped, Martin, & Fuchs, 2000; Hann et al., 1999; Macquart-Moulin et al., 2000), the magnitude of change (mean score changes > 40) for fatigue, pain, nausea and vomiting, appetite loss, and diarrhea was surprising. All of the symptoms occurred simultaneously. Future studies may explore symptom clusters in acutely ill patients undergoing HSCT. The small sample size in this study, however, precluded the ability to conduct such an analysis.

Given the magnitude of change in symptoms and functioning in patients undergoing HSCT, changes in life satisfaction were expected. Surprisingly, this did not occur. No statistically significant differences were found for overall life satisfaction or satisfaction with health and functioning, social and economic, or psychological or spiritual aspects of life. A previous study postulated that a lag time exists between experiencing actual changes in health status and assimilating the changes into an appraisal of life's circumstances (Hacker & Ferrans, 2003). The results from the current study provide further support for this notion. Patients may have expected to be acutely ill immediately following the high-dose chemotherapy and HSCT procedure. Because their expectations were consistent with reality, changes in life satisfaction did not occur. In Hacker and Ferrans' study, trends toward reductions in life satisfaction and satisfaction with health and functioning were identified two weeks following discharge from the hospital. In the current study, data were not collected following discharge from the hospital; therefore, the relationship between health status and life satisfaction cannot be fully examined. Nevertheless, the association among expectations, perceived health status, and life satisfaction merits further investigation.

Several additional limitations in the current study must be addressed because they may affect the interpretability of the findings. First, the sample size was small and conveniently selected, limiting generalizability. However, the fatigue, functional ability, and symptomatology findings are consistent with the literature, thereby strengthening the study results. The participants in this study were selected from two sites and treated by two different HSCT teams, further enhancing generalizability. The small sample size did not affect the ability to find statistically significant results that also were clinically important. In a previous study, the failure to find statistically significant results was attributed to small sample size and patient attrition (Hacker & Ferrans, 2003). The present study was designed to reduce subject burden, thereby limiting patient attrition, which was successful. Patient attrition was minimized, and statistically significant results were found for the major variables, including both instruments' measures of fatigue, physical activity, several aspects of functioning, and key symptoms expected in patients undergoing HSCT. Nonetheless, a sample size of 20 should be considered small, and further investigation using larger samples is warranted.

Implications for Nursing

Patients undergoing HSCT require considerable supportive nursing care immediately following the conditioning regimen and HSCT. Oncology nursing professionals, both clinicians and researchers, strive for effective symptom management to improve successful outcomes following intensive treatments for cancer. Maintaining or increasing levels of physical

activity may play a role in reducing fatigue and improving health status perceptions and QOL.

Conclusion

The HSCT procedure and high-dose chemotherapy with or without total body irradiation affect all aspects of patients' lives, particularly during the immediate post-transplant period. Immediately following the preparatory regimen for HSCT, patients can expect to experience increased fatigue, reduced physical activity, increased symptomatology, and diminished functional capacity. Moderate to large increases in cancer symptoms occurred in fatigue, pain, nausea and vomiting, appetite loss, diarrhea, and sleep disturbances. The symptoms occurred simultaneously in the acute post-transplant period. Deviations in health status perceptions, however, did not result in dissatisfaction with life.

The current study demonstrates the feasibility of collecting real-time fatigue and physical activity data in patients undergoing HSCT. Computerized real-time collection of fatigue data minimized biases associated with patient recall and allowed documentation of patient compliance. Most patients were able to provide real-time fatigue data even when experiencing multiple side effects from the preparatory regimen. Ecologic momentary assessment is a novel approach that holds substantial promise for investigating fatigue and other cancer symptoms.

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