Effects of Exercise on Fatigue, Sleep, and Performance: A Randomized Trial

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Purpose/Objectives: To compare usual care with a home-based individualized exercise program (HBIEP) in patients receiving intensive treatment for multiple myeloma (MM) and epoetin alfa therapy.

Design: Randomized trial with repeated measures of two groups (one experimental and one control) and an approximate 15-week experimental period.

Setting: Outpatient setting of the Myeloma Institute for Research and Therapy at the Rockfellow Cancer Center at the University of Arkansas for Medical Sciences.

Sample: 187 patients with newly diagnosed MM enrolled in a separate study evaluating effectiveness of the Total Therapy regimen, with or without thalidomide.

Methods: Measurements included the Profile of Mood States fatigue scale, Functional Assessment of Cancer Therapy–Fatigue, ActiGraph® recordings, 6-Minute Walk Test, and hemoglobin levels at baseline and before and after stem cell collection. Descriptive statistics were used to compare demographics and treatment effects, and repeated measures analysis of variance was used to determine effects of HBIEP.

Main Research Variables: Fatigue, nighttime sleep, performance (aerobic capacity) as dependent or outcome measures, and HBIEP combining strength building and aerobic exercise as the independent variable.

Findings: Both groups were equivalent for age, gender, race, receipt of thalidomide, hemoglobin levels, and type of treatment regimen for MM. No statistically significant differences existed among the experimental and control groups for fatigue, sleep, or performance (aerobic capacity). Statistically significant differences ($p < 0.05$) were found in each of the study outcomes for all patients as treatment progressed and patients experienced more fatigue and poorer nighttime sleep and performance (aerobic capacity).

Conclusions: The effect of exercise seemed to be minimal on decreasing fatigue, improving sleep, and improving performance (aerobic capacity).

Implications for Nursing: Exercise is safe and has physiologic benefits for patients undergoing MM treatment; exercise combined with epoetin alfa helped alleviate anemia.

Patients with multiple myeloma (MM) often receive intensive multidisciplinary treatment and experience multiorgan complications as a result of their disease and treatment (Coleman, Coon, et al., 2003; Coleman, Hall-Barrow, Coon, & Stewart, 2003). At least 60% of patients with MM are anemic (hemoglobin [Hb] < 12 g/dl) at diagnosis (International Myeloma Foundation, 2011), and almost all become anemic during treatment, often requiring red blood cell (RBC) transfusions (Knight, Wade, & Balducci, 2004). In patients with MM, epoetin alfa has been shown to reduce transfusions and increase Hb during chemotherapy (Barlogie & Beck, 1993). Anemia contributes to fatigue, the most common and distressing symptom for patients with cancer, and is reported in 80% of patients receiving chemotherapy for cancer (Brizel, Dodge, Clough, & Dewhirst, 1999; Glaspy et al., 2001; Silber et al., 1998).

Cancer-related fatigue is multidimensional, subjective, perceived as abnormal and distressing, and inadequately relieved by rest. Fatigue may lead patients to abandon treatment and can be so overwhelming that some patients say they would rather die (Curt et al., 2000). Insomnia frequently is related to fatigue in patients with cancer (Berger & Farr, 1999; Bower et al., 2000). The increase in daytime sleep and fatigue decreases daytime physical activity, leading to physiologic deconditioning and diminished activity tolerance (Winningham et al., 1994). Aerobic exercise improves sleep for healthy individuals (Petruzzello, Landers, Hatfield, Kubitz, & Salazar, 1991) and decreases fatigue for individuals with cancer (Dimeo, 2001). Therefore, exercise is recommended as an intervention for fatigue (Berger et al., 2010). A systematic review and meta-analysis reported that a set of 14 controlled trials of exercise after treatment had a

combined weighted mean effect size of –0.54 (–0.9 to –0.19; p = 0.003), but the intervention varied by duration, type, intensity, and frequency, and no specific intervention emerged as superior (Speck, Courneya, Mässe, Duval, & Schmitz, 2010). Location and supervision of exercise also varied, but home-based exercise may yield more significant results when compared with supervised programs (Jacobsen, Donavan, Vadaparampil, & Small, 2007). Patients with fatigue and muscle wasting may benefit from combined aerobic and resistance exercise (Strong, Karavatas, & Reicherter, 2006). Walking for exercise can incorporate steps inherent in daily activities, as well as steps spent in purposeful exercise activities; use of a pedometer may provide objective step counts to verify adherence or contradict patient self-report (Swenson, Nissen, & Henly, 2010).

Baseline activity may be related to physical activity at later points during treatment (Swenson et al., 2010) or may predict fatigue during treatment (Luctkar-Flude, Groll, Woodend, & Tranmer, 2009). Timing of the exercise intervention varies among studies, but it usually occurs during cancer treatment or after it has concluded. Performance, as shown by aerobic threshold, may improve with exercise (Dimeo, Schwartz, Wesel, Voigt, & Thiel, 2008). Earlier research also indicated that exercise during cancer treatment can improve performance as measured by patient self-report and 12-minute walk times (Mock et al., 2001).

Patients with cancer experience skeletal muscle wasting (Giordano et al., 2003); therefore, to achieve maximum benefit, the current study combined aerobic exercise with strength resistance training in a home-based individualized exercise program (HBIEP) and tested the hypothesis that HBIEP will improve cancer-related insomnia and cancer-related fatigue. Because anemia is a major factor influencing cancer-related fatigue, patients with MM received treatment for anemia.

The current study sought to compare usual care with HBIEP by incorporating aerobic and strength resistance training on fatigue, daytime and nighttime sleep, and performance (aerobic capacity) in patients receiving intensive treatment for MM and epoetin alfa therapy. In addition, the effects of exercise with epoetin alfa therapy on Hb levels were assessed.

Theory Base

Winningham's (1996) Theory of Cancer-Related Fatigue, which provided the theoretical rationale for the current study, contains three graphic models (the Winningham Psychobiological-Entropy Model of functioning, the energetics of functioning, and the fatigue-inertia spiral), as well as 10 propositions explaining fatigue in cancer. The essence of Winningham's theory

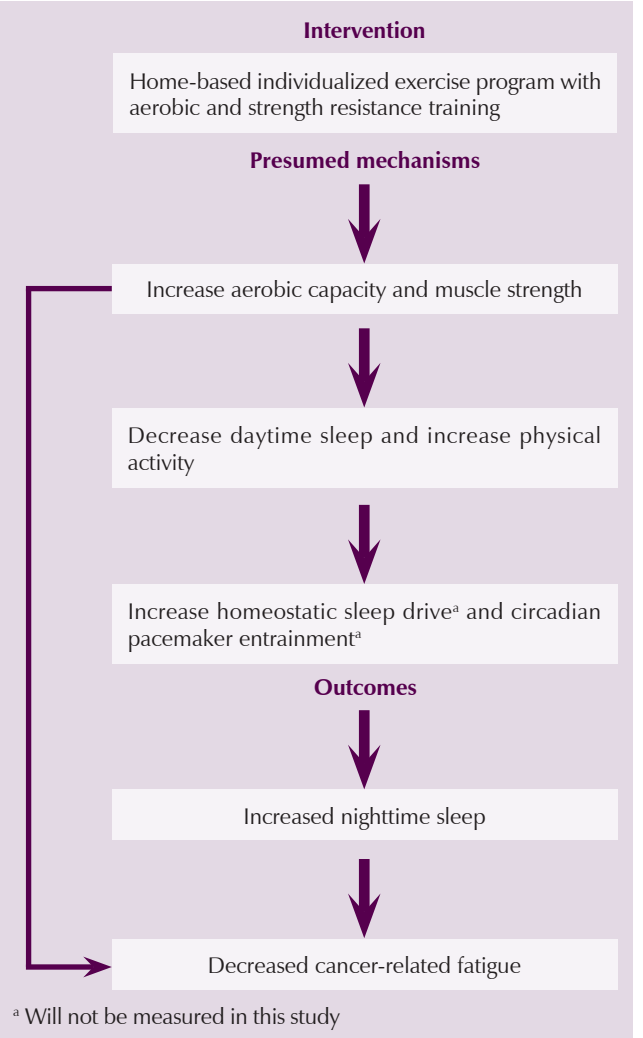

Figure 1. Conceptual Model: The Effects of Home-Based Intervention Exercise Program in Patients With Multiple Myeloma

as it pertains to the current study is that too much or too little rest and/or too much or too little exercise increases fatigue and results in decreased activity, which then leads to physiologic deconditioning and great feelings of fatigue. The resulting negative feedback loop causes a downward spiral toward disability. Appropriate management of symptoms, restorative rest, and increased exercise can reverse the spiral.

Figure 1 displays the conceptual model for the proposed test of the effectiveness of HBIEP. The two-process model proposes that sleep is regulated by a homeostatic process determined by sleep and waking that augments sleep propensity after curtailed sleep, or reduces sleep propensity after excess sleep, and a circadian process, a clocklike mechanism with alternating periods of high and low sleep propensity (Borbely, 2000). The homeostatic process rises at waking and declines during sleep and interacts with the circadian process. During usual conditions, individual

contributions of the circadian and homeostatic processes cannot be determined. Research protocols conducted in laboratory settings over time desynchronize the circadian and homeostatic processes and allow scientists to separate them. Those protocols support the two-process model, showing that the homeostatic sleep drive is greatest at sleep onset and facilitates sleep in the first half of the night. As the homeostatic sleep drive declines, the circadian drive for sleep becomes greatest, therefore, maintaining an elevated sleep drive through the end of the sleep episode. Together, the two processes generate consolidated nighttime sleep (Czeisler & Khalsa, 2000). The current study proposed that increased daytime sleep and physical inactivity harm the homeostatic sleep drive and entrainment of the circadian rhythm in patients with cancer, leading to decreased nighttime sleep. To be most effective, behavioral interventions, such as the HBIEP, should strengthen the homeostatic and circadian processes. The current study also proposed that aerobic and strength resistance training will increase aerobic capacity and muscle strength, leading to a subsequent increase in physical activity, which will strengthen circadian pacemaker entrainment. In addition, the increased physical activity will decrease daytime sleep and increase the homeostatic sleep drive.

Methods

The current study used a repeated-measures experimental design with a group that received the HBIEP, combining aerobic and strength resistance training, and the control group receiving the current best practice recommendation to walk 20 minutes three times a week (usual care). A 15-week experimental period was chosen based on the American College of Sports Medicine's (1991) recommendation that 15–20 weeks of regular exercise are necessary to acheive fitness benefits. Daytime and nighttime sleep, fatigue, and aerobic capacity were measured at three time periods during the MM treatment protocol: at baseline and before and after stem cell collection. Because patients in both groups were on prophylactic epoetin alfa, data were collected on Hb levels at the same time periods. Testing times corresponded with the times when patients returned for treatment.

Sample and Setting

The study occurred in the southern part of the United States at an international referral center that has seen over 10,000 patients with MM. Patients in the study population were newly diagnosed with MM and eligible for treatment with aggressive protocol that included tandem peripheral blood stem cell (PBSC) transplantations (see Table 1). The majority of the patients were well-educated and had greater motivation to exercise than the general population of patients with MM. Because they probably have read about the benefits, patients in the control group also were expected to be motivated to exercise. The intent of the intervention was to determine whether specific exercises are more effective in improving sleep and decreasing fatigue.

The treatment for MM was planned for the outpatient setting, and patients were admitted to the hospital only for severe complications of the disease or its treatment, or for insurance reasons. The protocol for treatment (Total Therapy II) for the first 125 patients included induction chemotherapy with VAD (vincristine, doxorubicin, and dexamethasone), DCEP (dexamethasone, cyclophosphamide, etoposide, and cisplatin), and CAD (cyclophosphamide, doxorubicin, and dexamethasone), and stem cell collection before high-dose melphalan followed by a PBSC transplantation.

About three months after the first transplantation, all patients received a second treatment with high-dose melphalan and stem cell transplantation. Half of the patients were randomized to receive thalidomide (same dosage and schedule) during induction, post-transplantation consolidation, and maintenance therapy (Barlogie, 2001).

The treatment regimen (Total Therapy III) for the remaining 62 patients included two cycles of VDTPACE (bortezomib, dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, and etoposide) with interim treatment of thalidomide and dexamethasone before high-dose melphalan and PBSC transplantation.

Table 1. Sample Characteristics by Study Group

	Usual Care (N = 92)			Exercise (N = 95)			
Characteristic	**$\bar{X}$**	**SD**	**Range**	**$\bar{X}$**	**SD**	**Range**	**p***
Age (years)	56.37	9.33	35–76	56.01	10.47	25–76	0.8
Characteristic	**n**		**%**	**n**		**%**	**p***
Gender							0.68
Female	37		40	41		43	
Male	55		60	54		57	
Race							0.36
Caucasian	85		92	84		88	
Other	7		8	11		12	
Total therapy							0.4
II	69		75	66		69	
III	23		25	29		31	
Thalidomide							0.28
No	40		43	34		36	
Yes	52		57	61		64	

* Chi-square test except t test for age

All patients on Total Therapy III received thalidomide. Stem cell collection occurred twice, after the first and second cycles of chemotherapy, for two high-dose melphalan treatments. Each melphalan treatment (one after the second cycle of VDTPACE and another about two to three months later) was followed by PBSC transplantation.

In addition to the treatment for MM, all patients who enrolled in the study received prophylactic recombinant epoetin alfa according to an investigational algorithm developed by the authors. The first 125 patients were treated according to an algorithm that allowed their Hb to reach 15 g/dl before dose reduction or delay. The algorithm was modified so that Hb reached 13 g/dl for men and 12 g/dl for women before dose reduction or delay for the subsequent enrolling 62 patients. The majority of patients with MM have anemia at initial presentation, 62% have a Hb level less than 12 g/dl, and 25% present with a Hb level less than 8.5 g/dl. The anemia is generally normochromic and normocytic and results from inadequate production of RBCs, presumably from displacement by excessive numbers of abnormal plasma cells, shortening of RBC survival, and renal insufficiency (Kyle, 1975). Patients are given epoetin alfa in an attempt to alleviate anemia, which is a factor in fatigue (Cella, 2002).

Inclusion and exclusion criteria: As patients enrolled in the aggressive treatment program, they were assessed for inclusion in the current study. Those who were not at high risk for impending pathologic fracture or cord compression, as determined by magnetic resonance imaging, other radiology reports, and physician assessments, were invited to participate in the study. Patients were excluded if they were unable to understand the intent of the study, were diagnosed with a major psychiatric illness, or had presence of a microcytic or macrocytic anemia, uncontrolled hypertension, red cell transfusions within two weeks of study enrollment, or recombinant epoetin alfa within eight weeks of study enrollment.

Randomization process: Patients who provided written consent were randomly assigned to either the HBIEP or a control group. The computerized randomization process, using the method of minimization (Pocock & Simon, 1975), stratified consenting patients according to age (60 years and younger or older than 60 years) and thalidomide status (yes or no) to make about equivalent groups for the variables, which are known to affect sleep (Barlogie et al., 2001; Clark, Edom, Larson, & Lindsey, 2001; Kanbayashi et al., 1999; Montgomery & Dennis, 2003; Morin, 1993; Tariman, 2003).

Sample size calculation: A sample size of 200 participants was calculated for a repeated-measures design, which has the advandtage of the baseline measurement for each patient serving his or her control. Therefore, statistical tests for the effects of exercise are based on intraindividual differences across repeated measures, which tend to have smaller standard deviations. Results from preliminary work provided estimates of the standard deviations and the sizes of anticipated effects of exercise. Based on that information, the sample size was calculated to yield 80% power for detecting a statistically significant effect (one-sided, $p < 0.05$) because of exercise.

Intervention and Control Conditions

Following baseline tests, patients assigned to the HBIEP received an individualized exercise prescription and the patients assigned to control received usual care as prescribed by their physicians. All patients enrolled in the study received instructions to remain active and walk at least 20 minutes three times a week.

Intervention: The majority of patients receiving treatment at the international referral center do not reside in the local area; therefore, the exercise program had to be performed without direct supervision and adaptable to home implementation, travel, and temporary housing situations. Patients assigned to the HBIEP received a set of color-coded exercise stretch bands with varying resistance and a notebook and videotape made by the authors to illustrate the exercises. The exercise program was developed by the researchers and consisted of three components: (a) daily stretching exercises for the hamstrings, shoulder rotation, calves, hip flexors, and triceps, (b) strength and resistance training for the extremities, and (c) aerobic walking. The strength resistance training, which occurred on alternating days from aerobic walking, consisted of biceps curls, triceps extensions (chair push-ups), chair stands, and hamstring strengthening.

Biceps curls are performed with the color-coded exercise stretch bands with handles at each end to make them easy to use. Triceps extensions (chair push-ups) are performed by sitting in a stationary chair that has sturdy arms and lifting the buttocks from the seat of the chair by pushing straight up on the chair arms without assistance from the legs. Chair stands are performed by sitting to the front of a stationary chair and, while keeping the back straight, slowly rising from the chair without assistance from the chair's arms, then slowly lowering back onto the chair. Hamstring strengthening is performed while sitting or standing supported, with the hip slightly extended, slowly bending each knee as far back as possible, and concentrating on feeling muscle contraction in the back of the thigh.

Intensity of training: Aerobic walking was done at a level that allowed patients to reach 65%–80% of their maximum heart rate. Patients used the Borg Scale, a simple method of subjectively rating exertion, to determine their rate of perceived exertion (RPE) each

time they exercised (Borg, 1998; Utter, n.d.). The RPE correlates with approximate heart rate (e.g., an RPE of 12 correlates with a pulse rate of about 120 beats per minute). Ratings from 11–13 (fairly light to somewhat difficult) meant patients had reached the desired training level, and they were asked to maintain that for as long as possible during the session. Participants were told to stop immediately if they became dizzy, became short of breath, or had pain while exercising. Strength resistance training was performed at an intensity of 60%–80% of the one repetition maximum (1RM), the maximum weight one can lift in a single repetition. The literature indicates that 80% of 1RM (about eight repetitions to fatigue) performed three days per week results in substantial increase in muscle strength and size. Lower intensity training (30%–50% of 1RM) results in only modest gains in strength (Fiatarone et al., 1994; McDonagh & Davies, 1984). Patients also used the Borg Scale to determine their RPE for strength training; a rating of 15–17 (difficult to very difficult) was desired, so patients were asked to perform each strength training exercise until they reached that level.

Exercise prescription: The exercise program was based on the assessment of patients' health and exercise histories, as well as strength levels and aerobic capacity determined during baseline testing. The exercise program was discussed, and the exercises were demonstrated by the investigators. After confirming that the patients could perform the exercises, the researchers stressed the importance of completing whatever portion of the exercise prescription patients were able to accomplish. They were asked to record their performance in an exercise log, which helped patients and allowed the researchers to track the frequency, intensity, and duration of the exercises performed. The patients faxed or mailed documentation of their weekly exercise performance, and the programs were altered to accommodate individual physical functioning.

Encouraging compliance with the exercise program: The researchers emphasized to the HBIEP group that they were making a commitment to follow the exercise program to the best of their ability. When patients were tested at baseline, family members or significant others were encouraged to attend and be included in the explanation of the testing and the exercise demonstrations because support is essential in maintaining an exercise program (Coleman, Hall-Barrow, et al., 2003; Wallace, Buckworth, Kirby, & Sherman, 2000). Patients were instructed to fit the exercise into their normal routine and to break up the exercises throughout the day to allow for flexibility. Staying out of crowds and away from people with colds or other infectious diseases was important because MM and its treatment weaken the immune system. Therefore, patients were encouraged to walk or jog on treadmills in their homes or outside in their neighborhoods and avoid exercising in gyms or malls when their white blood cell counts were low. As with most cancer treatments, patients receiving treatment for MM experience many side effects that may interfere with completing the exercise prescription (Coleman, Coon, et al., 2003). To keep patients involved in some activity, even during the worst time of their treatment, they were taught to tailor the exercise prescription to their ability (i.e., some patients only may have needed to complete eight chair stands throughout the day). Even a small amount of movement provided them with a task they could complete and feel successful about achieving. The most important part of the exercise program was keeping patients involved and performing some type of prescribed exercise. Participants were told to call their local physician and notify the researchers if they encountered a problem.

Weekly activity summary: All patients mailed or faxed an activity summary each week that helped the researchers counsel patients regarding their ability to exercise. If they were not able to complete their personal care because of some temporary complication, the intensity of their exercise program was decreased. Time spent with patients from each treatment group was about equal, whether at the treatment site or by telephone.

Measurements

Participants' sleep, fatigue, and performance (aerobic capacity) were measured at three different times: (a) just prior to beginning chemotherapy for all patients, (b) 10–12 weeks later, just prior to chemotherapy for stem cell mobilization in Total Therapy II patients or just before the second cycle of chemotherapy in Total Therapy III patients, and (c) about 3–4 weeks later when finishing stem cell collection in Total Therapy II patients and just prior to transplantation for Total Therapy III patients. Daytime and nighttime sleep were measured using **ActiGraph®** (Sadeh, Sharkey, & Carskadon, 1994). The ActiGraph has 85%–95% minute-by-minute agreement among activity-based sleep-wake scoring and traditional polysomnography-based scoring in healthy individuals (Ancoli-Israel et al., 2003; Sadeh et al., 1994). An additional sleep variable was percentage of time spent asleep in bed at night (sleep efficiency). Patients wore the ActiGraph for 72 hours at each testing period to decrease the effect of random variance, and they recorded their bedtimes and rise-times on a log during the three-day measurement periods.

The **Profile of Mood States** (**POMS**) fatigue-inertia rating scale (McNair, Lorr, & Droppleman, 1992) and the **Functional Assessment of Cancer Therapy–Fatigue** (**FACT-F**) questionnaire (Cella, 1997; Cella, Lai, Chang, Peterman, & Slavin, 2002) were used to assess fatigue. For the POMS fatigue-intertia scale, examination

of the individual items defining each mood scale supported content validity, and four areas of research provided evidence of the predictive and construct validity of the POMS. The internal consistency reliabilities were highly satisfactory, ranging from 0.87–0.95 (McNair et al., 1992). The FACT-F had demonstrated stability (r = 0.87) and strong internal consistency (Cronbach alpha = 0.95). Test-retest reliability coefficients showed stability (r = 0.84–0.9) (Cella, 1997; Yellen, Cella, Webster, Blendowski, & Kaplan, 1997). Scores range from 0–52, with higher scores indicating less fatigue. FACT-F scores correlate well with physical function scores, and researchers found that when the scores ranged from 45–52, fewer than 10% of participants reported they were very limited in climbing several flights of stairs.

The current study used the **6-Minute Walk Test**, a simple, submaximal exercise test that measures the distance walked on a level surface in six minutes to assess performance (aerobic capacity) (Chuang, Lin, & Wasserman, 2001; Hamilton & Haennel, 2000; Riley, McParland, Stanford, & Nicholls, 1992; Zugck et al., 2000). The test has been linearly related to maximum metabolic equivalents (r = 0.687, p = 0.001), which supported its validity, and the 6-Minute Walk Test had a strong test-retest reliability (intraclass correlation = 0.97) (Hamilton & Haennel, 2000). Because all participants received epoetin alfa therapy, data were collected on Hb levels. A more detailed description of the instruments and measurements is reported in Coleman et al. (2010).

Data Analysis

The descriptive statistics for the participants in each group were calculated to compare the groups' baseline demographics and Hb levels with analysis of variance (ANOVA) and chi-square analyses. Although each group was stratified based on age and thalidomide status and included equal numbers of patients based on these variables, the distribution of the participants in the groups based on the variable was checked as well. Repeated measures ANOVA (RMANOVA) was used to determine the effects of HBIEP on fatigue, sleep, and performance (aerobic capacity). Fatigue scores from the FACT-F and the POMS fatigue-inertia scale were highly correlated (Pearson r = 0.84); only FACT-F scores were used for fatigue in the RMANOVA. The between groups variable was usual care versus exercise and the within groups variables were trial with three measures. The dependent variables were the fatigue scores, minutes of daytime and nighttime sleep, sleep efficiency, distance walked in six minutes, and Hb levels. Because compliance with the HBIEP would affect results, a qualitative analysis of the data was conducted from the weekly activity reports submitted by participants in both groups. If participants in the exercise group gave no indication that they had exercised, they were removed from the secondary analysis. Likewise, if participants in the control group indicated that they had exercised beyond walking 20 minutes, three times a week, they also were removed from the secondary analysis. That secondary analysis was conducted to assist in interpretation of the findings.

Findings

The HBIEP group had more nighttime sleep and a farther six-minute walk than the control group, although differences were not statistically significant. Table 2 shows all of the results for each of the three test times. The only statistically significant results were for test time ($p < 0.005$) with all patients becoming more fatigued, sleeping less at night, and experiencing a decline in six-minute walk distance with more treatment. The control and HBIEP groups had similar Hb levels for each of the test times. No main effect differences existed for the groups. The groups' results were similar across comparable trials. For example, for the first trial measure, the FACT-F score mean was 33.92 for the control group and 37.51 for the HBIEP group. Similarly, for the second trial, the comparable findings were 34.47 and 37.5, respectively; for the third trial, the results were 31.71 and 31.34. The results were neither statistically significant nor, more importantly, clinically significant.

A qualitative analysis of the weekly exercise and activity reports showed that four patients in the HBIEP group did not exercise at all and that 22 patients in the control group had excercised beyond what was required of them. The latter group had primarily used walking as their exercise activity, although some had gone to a gym for more strengthening exercises. Removing those patients from the analysis had no effect on the RMANOVA results. Overall, the incidence of serious adverse effects was similar for the control and HBIEP groups (Coleman et al., 2008).

Using baseline data, the results have been published of a regression analysis with FACT-F as the dependent variable and age, gender, stage of disease, Hb at baseline, nighttime sleep, sleep efficiency, pain rating, POMS Total Mood Disturbance Score, 6-Minute Walk Test, and strength test as the independent variables in the model (Coleman et al., 2010). The model, including all of the variables, was statistically significant ($p > 0.0005$). The measure of effect is adjusted $R^2 = 0.58$. According to Cohen (1992), this is a large effect (0.01 is the minimum for a small effect, 0.09 for a moderate effect, and 0.25 for a large effect). This model seemed to support the current study's hypothesis. Because the study sample was only 13 patients away from the estimated 200 needed, the sample size

Table 2. Fatigue, Sleep, and 6-Minute Walk Test Scores and Hemoglobin by Test Time

Test Time	Control (N = 75) $\bar{X}$	SD	Min	Max	n	HBIEP (N = 91) $\bar{X}$	SD	Min	Max	n	p[a]
FACT Fatigue score											0.05[a]
1	33.92	11.9	6	51	74	37.51	11.36	10	52	91	
2	34.47	11.28	9	52	64	37.5	8.74	9	52	78	
3	31.71	14	0	52	61	31.34	12.78	3	50	80	
POMS Fatigue score											0.11
1	9.45	6.46	0	28	74	7.82	6.51	0	26	91	
2	9.17	5.97	0	23	64	7.69	4.96	0	22	78	
3	10.92	7.18	0	28	61	10.63	7.19	0	26	80	
Minutes of nighttime sleep											0.28
1	424.3	101.94	58	637.9	71	406.47	101.29	71	718.3	86	
2	449.09	103.74	56	608	62	411.25	96.3	189	679	76	
3	414.33	111.94	158.7	658	58	411.7	110.02	104.7	590.33	74	
Sleep efficiency											0.47
1	81.39	14.01	11.4	98.5	71	79.7	15	14.6	97.7	86	
2	82.49	15.39	12	99.2	62	81.19	13.31	36.7	99.7	76	
3	76.57	20.51	9	97.85	58	77.79	18.96	10.1	97.32	74	
Minutes of daytime sleep											0.71
1	100.89	92.12	0.7	474	71	95.14	98.5	0	444.3	86	
2	140.04	125.17	2.33	790	62	115.97	95.46	5	452.33	76	
3	114	97.45	0	451.7	58	113.17	93.59	0	462	74	
Distance in number of feet walked in six minutes											0.51
1	1,579.11	358.52	504	2,314	74	1,621.62	443.88	535	2,563	90	
2	1,627.18	413.74	131	2,624	62	1,675.13	426.23	160	2,610	78	
3	1,545.07	443.69	236	2,468	55	1,594.69	497.84	0	2,594	74	
Hemoglobin level											0.11
1	11.79	1.64	8.3	16.5	74	11.34	1.88	7.3	15.8	91	
2	12.14	1.35	9.1	15.3	74	12.26	1.46	9	16.1	91	
3	10.6	1.7	8	15.7	74	10.57	1.7	8	15.7	91	

[a] By repeated measures analysis of variance

FACT—Functional Assessment of Cancer Therapy; HBIEP—home-based intervention exercise program; Max—maximum; Min—minimum; POMS—Profile of Mood States

seemed adequate to detect any important difference between groups.

Limitations

The patients self-reported their compliance with the HBIEP. Observation of the exercise and activity was not possible because this was a home-based program. Also, patients in the control group were not discouraged from exercising. Researchers assumed that patients who were exercising would perform better on the 6-Minute Walk Test than those not exercising. Because of central lines and the risk of pathologic fracture, all patients could not perform the strength tests. Only 18 of the 88 patients could perform the strength test at baseline and results of that test have been reported (Coleman et al., 2010). Anemia is present at baseline in the majority of patients with MM and all participants would become anemic with treatment so, ethically, each group received treatment for anemia, potentially limiting results.

Conclusions

Results seem to indicate that no benefit was derived from exercise for cancer-related fatigue and insomnia. As expected, results showed that patients became significantly more fatigued, slept less at night, and experienced a decline in performance with more treatment. However, the HBIEP group, compared to the control group, required significantly fewer RBC transfusions to maintain a similar Hb level, significantly fewer platelet transfusions to maintain an adequate platelet count, significantly fewer attempts at stem cell collection, and significantly fewer days to collect stem cells for transplantation (Bonferroni adjusted $p < 0.025$) (Coleman et al., 2008). Therefore, exercise did have a

large effect when combined with epoetin alfa therapy in decreasing cancer-related anemia and improving cell count recovery after high-dose chemotherapy. Fewer transfusions and improved stem cell collection are major benefits to patients and the healthcare economy. As a result, exercise in combination with medical treatment for anemia does affect cancer-related fatigue by helping to alleviate anemia. In addition, the HBIEP was a safe intervention for patients in the study.

Cancer-Related Insomnia and Exercise

Sleep problems may be present prior to cancer treatment and may be influenced by cancer or its treatments. Patients in the current study had wide variations in sleep at baseline, including mean nighttime sleep of 6.9 hours, an average of 12 awakenings at night, and 19% of total sleep time occurring as daytime naps (Coleman et al., 2010). Sleep problems increased as treatment persisted. A few studies have addressed exercise in relation to sleep problems, but insufficient evidence is available for exact exercise prescription (Berger, 2009).

Cancer-Related Fatigue and Exercise

Cancer rehabilitation exercise may result in improved performance during the exercise intervention period and facilitate sustained improvement in subsequent weeks or months (De Backer et al., 2008; Mustian et al., 2009). Exercise occurred during treatment in the current study, and no attempt was made to extrapolate possible sustained effects or sustained exercise after the intervention period.

Exercise Combined With Treatment of Anemia

Using exercise and erythropoiesis-stimulating agents to help manage anemia may decrease transfusion needs and even improve stem cell collection (Coleman et al., 2008), decreasing the physical burden of treatment for patients. Although the current study used Hb levels as a measure of anemia to predict or explain fatigue, some research indicates that C-reactive protein may be more predictive of fatigue than Hb (Booker, Olson, Pilarski, Noon, & Bahlis, 2009), and baseline anemia may be an indicator of malnutrition leading to fatigue in patients receiving cancer (Cruciani et al., 2006; Nair et al., 2008). In those instances, the inclusion of nutritional therapy or dietary counseling might bring additional reduction in fatigue.

Implications for Nursing

The presence of fatigue before treatment may predict fatigue in patients during treatment (Wielgus, Berger, & Hertzog, 2009). The National Comprehensive Cancer Network's guidelines for cancer-related fatigue recommend assessment for fatigue, sleep disturbance, anemia, and deconditioning before treatment (Berger et al., 2010). In addition, energy conservation measures as well as endurance and resistance exercise should be considered, but rehabilitation therapy may be needed for deconditioned patients (Berger et al., 2010). Exercise must be tailored individually, keeping in mind the patient's disease stage, presence or absence of bone lesions, and values and preferences. Fatigue, deconditioning, side effects or precautions with treatment (surgery, radiation, chemotherapy), lack of self-confidence, and lack of motivation are among the factors that may deter patients from continued exercise after formal or structured exercise interventions end (Blaney et al., 2010). Patients need to be told they are in charge of their exercise program and that sources are available for counseling. Promoting a positive attitude toward exercise, providing education to help maximize strengths and decrease barriers to exercise, and involving patients in choosing an appropriate type and amount of exercise may facilitate adherence and better outcomes (Adkins, 2009).

Working with and advocating for patients will help tailor exercise prescriptions to provide effective, safe, physical activity and provide supportive care for medical treatment such as epoetin alfa for patients with MM. Results of this study are essentially negative and do not provide evidence that the HBIEP combining muscle strengthening and aerobic walking exercises decrease fatigue. However, an analysis of the data using the 125 patients enrolled in the Total Therapy II treatment protocol from the same study showed that exercise reduced the number of RBC transfusions. Therefore, the HBIEP helped alleviate the anemia, a major factor of fatigue (Coleman et al., 2008).

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