EXERCISE, AND ACTIVITY PATTERNS IN CANCER PATIENTS AFTER RECENT ALLOGENEIC BONE MARROW TRANSPLATATION

A DISSERTATION

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE

DEGREE OF DOCTOR OF PHILOSOPHY

IN THE GRADUATE SCHOOL OF THE

TEXAS WOMAN'S UNIVERSITY

COLLEGE OF HEALTH SCIENCES

BY

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DENTON, TEXAS

MAY, 2006

ACKNOWLEDGEMENTS

My most heartfelt gratitude to the members of my dissertation committee: Dr. William Bartlett, Dr. Maureen Simmonds, Dr. Sharon Olson, Dr. Karen Anderson, and Dr. Toni Roddey. Their encouragement, support and feedback were invaluable in the completion of this dissertation. I consider them my academic parents, patiently guiding and challenging me, and never accepting less than my best efforts.

I want to thank my family for all of their love and support. To my Dad, who did not blink when his only child told him that she wanted to move halfway around the world to go to graduate school. I hope I have made you proud.

My dear Matthew who kept me sane, made me laugh and has been a source of love and support. To Andrea Shapiro, who proofread my dissertation and made it better.

I am indebted to Ms. Pam Massey, PT, MS, without whom this dissertation would not have gotten off the ground. Lastly, my thanks to the patients at M. D, Anderson Cancer Center, who allowed me to poke and prod and intrude into their lives. You are all inspiring.

ABSTRACT

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MAY, 2006

Exercise following autologous bone marrow/ peripheral blood stem cell transplants (BMT/PBSCT) may decrease fatigue and loss of physical function that usually occur post-transplant. However, there is little empirical data regarding the effect of exercise on activity levels and symptom severity following allogeneic BMT. The purposes of this dissertation was to perform an exploratory examination of the effectiveness of short-term clinician-directed and self-directed exercise programs in recent allogeneic BMT/PBSCT patients using multi-dimensional outcomes; to examine activity and sleep patterns in post-BMT or peripheral stem cell transplant patients using actigraphy, and to describe through a series of case reports changes in physical performance, activity patterns and quality of life during participation in a supervised or a self-directed exercise program. Forty-four (44) patients with a primary cancer diagnosis of lymphoma or leukemia, within 6 months of an allogeneic BMT/PBSCT participated. They were randomly assigned to a self-directed exercise group, which received instruction on a home exercise program and walking regimen, or a clinician-directed exercise group, which performed mixed aerobic-resistive exercises for 45-60 min., thrice a week for 4 weeks. Subjects were evaluated at baseline, 4 and 8 weeks using a physical performance battery, Brief Fatigue Inventory, M.D. Anderson Symptom Inventory, and Functional Assessment of Cancer Therapy – Bone Marrow Transplant (FACT-BMT). Objective sleep and wake activity data were obtained through continuous monitoring using an actigraph. Marginal power was observed for group differences, and selected data analyses were performed on a combined exercise group. Within the short time period measured, it appears that both clinician-directed and self-directed exercise regimens are beneficial and may result in improvements in physical performance and quality of life, and a reduction in fatigue severity. Significant relationships noted between self-reported measures point to the possible influence of fatigue and/or BMT-related symptomatology on physical and functional aspects of quality of life. Polyphasic activity patterns, with longer than normal sleep durations and shorter than normal sleep episode lengths were observed via actigraphy. Future studies with larger samples over a longer period of time are warranted for statistical relevance.

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CHAPTER 1

INTRODUCTION

Bone marrow and peripheral blood stem cell transplantation (BMT/PBSCT) represents the treatment of choice for many patients with hematological cancers such as leukemias, lymphomas, myelomas and some solid tumor cancers like breast and ovarian cancers. These procedures are being performed with increasing frequency since their introduction about 30 years ago: currently, according to the International Bone Marrow Transplant Registry (IBMTR), at least 55,000 autologous and allogeneic marrow transplants are performed annually worldwide.[1] What was once a salvage procedure for patients with resistant and end stage malignancies is now generally performed earlier in the disease course, thanks to improved understanding and management of complications, new pharmacological agents, and broadening of the eligibility criteria for transplantation.

Despite the benefits associated with BMT, e.g., improved relapse-free survival, there are also numerous associated sequelae, such as pancytopenias, fatigue, and cardiopulmonary toxicities that may limit patients' function and activities. These transplant-related morbidities are particularly pronounced in patients undergoing allogeneic BMTs. [2-4]

Physical exercise as a rehabilitation intervention for the oncological population has received growing interest. Cancer patients and survivors who participate in exercise and physical activity have shown improvements in mobility, physical function, cancer-related symptom severity, emotional distress, and quality of life.[5-17] Among patients following autologous bone marrow transplantation, exercise has been shown to decrease the levels of fatigue and treatment-related complications as well as attenuate the loss of physical function that usually occurs.[18-26] However, there is a paucity of empirical data regarding the effect of exercise on activity levels and symptom severity following allogeneic BMT, especially in the recent (less than 6 months post-BMT) BMT population.

Much of the literature has focused on supervised aerobic exercise programs. In light of the increasing emphasis on self-management, and given the complex nature of cancer following BMT, there is a need to examine and compare different types of exercise regimens or conditions (i.e., supervised vs. unsupervised) in order to determine regimens that work best. As it has been hypothesized that resistance- type exercises may have a possible muscle protein-sparing effect, as well as positive effects on risk factors associated with cancer,[18, 27] examining an exercise program consisting of aerobic and resistance exercises would be beneficial.

An accurate means of monitoring and measuring exercise participation and other physical activity completed is essential. Monitoring fluctuating symptoms such as fatigue and pain, as well as patient participation in the intervention, often requires frequent measurements to ensure accuracy.

Frequent measurements, however, may be time-consuming and burdensome to the patient, and may result in patient non-adherence to the intervention.

A method that has been generating interest of late as a direct, non-invasive, long-term indicator of activity is the use of activity monitors, or actigraphs. Previous studies using actigraphs have shown fluctuating patterns of lowered activity and disturbed sleep in both cancer patients receiving chemotherapy and/or radiation therapy. However, there is no quantitative information regarding baseline activity levels in the BMT population.

The purposes of this study are to:

1. perform a preliminary analysis of the effectiveness of short term supervised and unsupervised exercise treatment programs in terms of multi-dimensional outcomes. The outcome measures will include: clinician-measured physical performance tests, patient self-reports, and actigraphy.
2. determine the influence of clinical and demographic variables on treatment outcomes.
3. examine activity and sleep patterns in post-BMT or peripheral stem cell transplant patients using actigraphy.
4. describe through a series of case reports changes in physical performance, activity patterns and quality of life during participation in a supervised or a self-directed exercise program.

Research Hypotheses

Our hypothesis is that there will be a difference in physical performance, symptom severity, quality of life, and activity level in patients who participate in a supervised exercise program compared to those who participate in a self-directed exercise program. With respect to activity levels, we predict that there will be a difference in mean actigraphy scores and sleep-wake patterns between the two groups. We hypothesize that factors that could influence physical performance and adherence will include age, pre-transplant activity level, fatigue, and symptom severity. Moreover, patients will exhibit irregular, fluctuating, sleep and wake patterns. There will be a relationship between physical performance measures, self-report and actigraphy scores in this population.

Summary of Chapters

Chapter 2 presents an overview of the process of bone marrow/ peripheral stem cell transplantation as well as a systematic review of the literature on exercise and activity in patients following bone marrow/ peripheral stem cell transplantation. The use of actigraphy as a form of activity measurement will also be examined.

Chapter 3 contains a summary of descriptive results from the study. This chapter outlines and describes initial results of the effects of a short-term clinician-directed and self-directed exercise program in terms of multi-dimensional outcomes. These multi-dimensional outcomes consist of physical performance measures, as well as patient self-reports. This chapter also attempts to identify characteristics related to improved physical performance and quality of life among patients after recent allogeneic bone marrow transplantation.

Chapter 4 describes and discusses selected activity and sleep characteristics of a subgroup of subjects participating in a clinician-directed or self-directed exercise program. Aside from a thorough graphical analysis of the data from the actigraph, related self-report measures on fatigue and sleep variables are obtained and reported.

Chapter 5 provides an in-depth description of the changes over time in physical performance, fatigue, and activity and sleep patterns during participation in a supervised or self-directed exercise program. This was accomplished through a case series.

Chapter 6 summarizes this thesis' key results, conclusions and directions for further research.

The appendices include a detailed summary of the methodology used in this dissertation. As Chapters 3 – 5 describe specific parts of the general methodology, this appendix delineates the entire methodology for the work presented here. The appendices also includes details on subject recruitment, procedures, and instruments and outcome measures used.

CHAPTER II

REVIEW OF THE LITERATURE

Bone Marrow Transplantation

Injecting or feeding human bone marrow or spleen extracts into patients as a treatment for a variety of diseases, such as anemias or leukemias, has been reported on an irregular basis since the late 19th century.[28] However, more attention was paid to perfecting the techniques to harvest and administer the marrow cells, as well as identifying conditions to which bone marrow transplants could be applied, than to dealing with possible treatment complications or potential benefits to patients. In a review of reported bone marrow transplants published in 1970, of the approximately 200 patients that were evaluated, more than 50% of the patients had failed to engraft.[29]

In the intervening years, thousands of patients have received bone marrow or hematopoietic stem cell transplants as a treatment for many diseases. This has been mainly due to the refinement of criteria for performing transplants, improved techniques in histocompatibility testing and hemotopoietic stem cell collection, and better supportive care (e.g., transfusion support, pharmacological agents).[30] Currently, an estimated 55,000 autologous and allogeneic bone marrow transplants are performed every year worldwide, with a growth rate of about 10- 15% per year.[1]

The basis for blood and bone marrow transplantations lies in the assumption that patients with hematological malignancies or immunological disorders are expected to be cured if the stem cells that give rise to defective blood cells and cells of the immune system are replaced by healthy cells from a donor. Also, the use of hematopoietic cell transplantation allows for the overcoming of myelosuppression, which is the dose-limiting constraint for many chemotherapeutic regimens. By overcoming myelosuppression ("rescue"), drug doses can then be increased, which in turn theoretically leads to an increased cure rate. In addition, hematopoeitic stem cells serve as vehicles for carrying genes that generate products lacking in a patient.[31]

Types of Transplant

There are different types of bone marrow or peripheral blood stem cell transplants (BMT/PBSCT), depending on the source of the donor cells. Grafts are generally classified as autologous or allogeneic. In an autologous transplant, the bone marrow or blood stem cells come from the patients themselves. Donor cells are sourced through either the bone marrow or through peripheral blood. These cells are taken from the patient by either bone marrow collection or apheresis for peripheral blood stem cells and then re-infused back into the patient. Bone marrow is harvested from the posterior superior iliac crests by multiple aspirations while the patient is under general anesthesia.[32] Apheresis is performed with a large-bore catheter in the subclavian vein, usually with local or absent anesthesia.[32] In certain cases, such as if the neoplasm involves the bone or bone marrow, or if the patient is unable to undergo general anesthesia, peripheral blood stem cells may be the preferred source of stem cells.[33] Engraftment of the re-infused stem cells succeeds when they reach the marrow and begin reproducing new blood cells. Autologous grafts are generally performed in the absence of a histo-compatible match, or for certain leukemias.

In an allogeneic transplant, the bone marrow or stem cells come from either a genetically-matched donor, usually a sibling, parent or identical twin, or from an unrelated matched donor. In the latter case, these donors (or matched unrelated donors, MUDs) are usually found through national bone marrow registries. Matching of donor and transplant recipient involves typing human leukocyte antigen (HLA) tissue. The more antigens that match, the better the chances that the donated marrow will engraft.[34] Similar to autologous transplants, donor cells can be collected from bone marrow or peripheral blood stem cells. Another source of stem cells is from umbilical cord blood, harvested immediately after the delivery of an infant. Cord blood is considered an attractive stem cell source because it contains stem cells that reproduce into mature, functioning blood cells more quickly and more effectively than stem cells taken from adults. Also, cord blood, being of fetal origin, has a reduced immuno-competence that may make it less likely to be susceptible to graft-versus-host-disease (GVHD).[34] GVHD is a potentially devastating complication of allogeneic bone marrow and stem cell transplants wherein the healthy donor's immune cells in the transplanted marrow recognize the patient's tissues as foreign and attacks the patient's vital organs. However, the relatively small number of cells in cord blood limits its use to pediatric recipients or in combination with other sources of donor cells. Prior to bone marrow or stem cell transplantation, patients often undergo high-dose chemotherapy (HDC), sometimes together with total body irradiation.[34, 35] The goals of this intensive therapy are to destroy all cancerous cells, to create "space" within the bone for new marrow cells (i.e., micro-environment which allows the infused cells to grow and engraft), and to purge remaining immunologically competent host cells that might result in the rejection of the transplant, especially if the patient undergoes an allogeneic transplant.[36, 35]

About two-thirds of reported BMT/PBSCTs are autologous transplants.[30] Graft failures are less likely in autologous transplantations because the patient's own cells are not subject to rejection. However, relapse of the disease is also more likely to occur than in allogeneic transplants.[3, 33, 37, 38] On the other hand, treatment-related morbidity and mortality is more likely with allogeneic transplants.[3, 38] According to data from the International Bone Marrow Transplant Registry, the most common indication for autologous bone marrow transplants were multiple myelomas and lymphomas, and the most common indication for allogeneic transplants were leukemias.[1] Survival rates for patients who undergo bone marrow transplants vary with type of disease, as well as other factors including age of the patient, whether the patient achieved remission with conventional therapy, and whether the disease relapsed. Generally, younger patients, patients who are HLA-identical, patients who undergo the transplantation after first remission, and patients who have the transplant done within 1 year of diagnosis, have more favorable probabilities of survival. Three-year survival rates ranging from about 40% to 70% have been reported for leukemias and lymphomas.[39, 1, 40, 41]

Consequences following BMT

Although BMT/PBSCT has been successfully used to treat many potentially life-threatening conditions, notably many forms of cancer, it has also been associated with significant physical and psychological sequelae. These side- effects are often observed throughout the transplantation experience, starting from pre-transplantation. Many patients who undergo bone marrow transplant will already have undergone previous regimens of chemotherapy and/or radiation therapy, and thus may have already-existing declines in function.[35] In addition, bone marrow ablation results in cytopenia, with its associated concerns of developing anemia and infections. Recipients of allogeneic transplants run the risk of contracting GVHD. Generally, the lesser the match of the allogeneic graft, the greater the risk in contracting GVHD.[34, 42] Hence, recipients of transplants from matched unrelated donors are the most susceptible to GVHD. It has been reported that allogeneic transplants have up to a 50% risk of contracting acute GVHD if they receive donor cells from an HLA-identical sibling donor, and up to an 80% risk if the donor cells are from a matched unrelated donor.[43, 44]

Acutely, patients receiving allogeneic transplants are prone to infections because of neutropenia and/or prophylactic immunosuppressive therapy given to prevent GVHD.[44] The effects of GVHD can range from a minor skin irritation to liver failure or death.[34] Acute GVHD typically develops within the first three months following transplantation and usually involves the skin, digestive tract, and liver.[45, 44] One of the first signs to appear is a maculopapular rash on the trunk, palms, soles, or ears that may progress to generalized desquamation of the skin in severe cases.[45] GVHD of the gut often manifests as diarrhea, nausea and vomiting, and abdominal cramps.[44] Chronic GVHD most frequently develops three to six months post-transplant. The clinical manifestations are wide-ranging, and include skin lesions (erythema, depigmentation), dryness of the mouth and eyes, and hepatic and gastrointestinal involvement.[45, 44, 46] GVHD is typically managed through the use of high-dose corticosteroids, with muscle atrophy and steroid myopathy, or the weakening of proximal muscle groups, being major side- effects associated with its use.[47, 35] Chronic GVHD may persist in many patients up to at least twelve months after allogeneic transplant. Lenssen et al. reported that there was evidence of chronic GVHD in 63% of 192 allogeneic marrow transplant patients evaluated a year post-transplant, with 44% of these patients with severe enough GVHD that they needed immunosuppressive therapy.[48] Many of these patients also reported nutrition-related complaints such as oral sensitivity, xerostomia, and anorexia.[48] Other late complications associated with bone marrow transplants, allogeneic transplants in particular, include cataract formation, obstructive pulmonary disease, osteoporosis, and secondary cancers such as melanoma, thyroid, bone, and connective tissue cancers.[49, 44, 46]

Fatigue and loss of physical performance have been cited as common symptoms associated with BMT/PBSCT. It was reported that the physical performance of 70% of 89 patients being considered for PBSCT was classified as “poor” or “very poor” according to guidelines of the American College of Sports Medicine (ACSM).[50] Syrjala et al., using global quality of life questionnaires, reported that 40% of their patients needed up to a year to recover full physical function; at two years post-transplant, approximately 30% of the patients were unable to go back to full-time work due to lack of stamina.[51] A multi-center study found that of 200 patients interviewed at least a year post-transplant, 78% reported feeling fatigued, and 76% reported limitations in their ability to engage in vigorous physical activity.[52] Other problems reported include: reduced cardiopulmonary functional capacity, difficulty sleeping, dyspnea, nausea, increased anxiety, depression, psychological distress and compromised quality of life (QOL) relative to premorbid status.[53, 52, 54-57]

Complications experienced following the transplantation process have often been described as being similar to, but may be more severe than, those seen following routine chemotherapy, due to the higher doses and combination of chemotherapeutic agents used.[58, 59, 35] Even for long-term survivors of hematopoietic stem cell transplants, significant long-standing effects were reported in several aspects of their quality of life. Knobel and colleagues reported that fatigue, both physical and mental, was a very common complaint up to ten years post-transplantation.[60] Andrykowski and colleagues interviewed more than 600 autologous and allogeneic hematopoietic long-term stem cell transplant survivors who were, on average, seven years post-transplant.[61] The survivors reported poorer physical functioning, greater fatigue and more pain, and social adjustment and sleep problems, compared to a cohort of age-matched healthy controls. They perceived their health to be worse than the typical person their age. In contrast though, they reported greater psychological growth. This finding is consistent with other studies, which found that many cancer survivors often report greater empathy, improved interpersonal relationships and enhanced spirituality.[62-64] It has been theorized that diseases such as cancer, as well as the transplantation process, may be perceived as traumatic stressors, which then trigger both negative (e.g., poorer physical functioning, distress, etc.) and positive (e.g., closer interpersonal relationships, etc.) outcomes.[62, 65]

Role of Exercise in Cancer and Bone Marrow Transplantation

As physical and functional well-being are essential aspects of quality of life, it is important to explore interventions which could reduce the negative effects of BMT/PBSCT. An intervention that may address the broad range of issues following BMT/PBSCT is exercise. It has been receiving belated attention in the BMT/PBSCT population. The rationale for exercise as a rehabilitation intervention is strong. Physical exercise in the non-diseased population is associated with such benefits as increased cardiovascular and pulmonary fitness, as well as improved psychological well-being.[66-70] There is also strong evidence to suggest that exercise is favorable for the rehabilitation of patients with chronic diseases such as hypertension, diabetes, pulmonary disease, and arthritis.[71-74] Until fairly recently, the role of exercise in oncological rehabilitation programs has been mostly restricted to treatment addressing specific impairments caused, for example, by amputation or other surgical interventions. However, this attitude concerning the limited use of exercise in patients with cancer is changing. Research now exists which demonstrates the effectiveness of exercise specifically for adult cancer patients and survivors. Physical activity during and after cancer treatment has been associated with improved mobility, physical or cardiovascular performance, and quality of life, as well as decreased levels of fatigue and nausea.[5-17] Participants who exercised also reported less anxiety, depression, distress and difficulty sleeping.[75, 76, 9] Moreover, on a cellular level, studies in various cancer patient populations suggest that moderate exercise resulted in immunologic benefits such as improved NK cell cytolytic activity, monocyte function, and proportion of circulating granulocytes.[77-80] It also resulted in a pro-inflammatory response, i.e., decreased antagonist/cytokine ratio, which has been theorized to be potentially associated with decreased rates of infection or relapse.[81]

Many of the exercise protocols used in the studies consisted of cardiovascular training, mainly walking or cycling programs,[5, 6, 75, 7, 76, 79, 8-10, 13, 17] but there were a few that consisted of resistance training [14, 16] or a combination of cardiovascular and resistance training. [82, 11, 12, 15] Most of the studies that used a combined cardiovascular and resistance training protocol also included other elements. Kolden and colleagues' protocol included flexibility exercises as well; [11] Adamsen and colleagues used a protocol that they termed "body package," where high intensity aerobic and resistive exercises (60-100% of maximum heart rate and 85-95% of 1-RM) were alternated with low intensity activities like massage, relaxation and body awareness [12]. Young-McCaughan and colleagues' protocol also included educational sessions on cancer therapies, sleep, spiritual health, and health assessment [15]. The exercise procedures used ranged from self-directed or home-based walking programs [5, 75, 8-10, 13, 17] to structured programs that were closely supervised.[6, 7, 79, 11, 12, 14-16]

In a review of exercise intervention studies in cancer patients published by 2004 and appearing in the Medline database, Galvao and Newton noted it is becoming evident that while exercise is associated with many positive physiological and psychological benefits for cancer patients and survivors, many of the studies reviewed were still lacking in certain aspects.[83] Many studies were not randomized trials and used small sample sizes. These limitations may be in part due to the challenges of recruiting and following up on patients who may also be receiving added treatment interventions or have other physical or psychological issues related to cancer. For patients following BMT/PBSCT, there is a small but growing number of studies that have reported that exercise post- BMT/PBSCT has favorable effects on physical performance, fatigue, hemoglobin concentration, loss of muscle mass, duration of neutropenia and thrombocytopenia, and length of hospitalization.[18-21, 7, 22-25, 84, 26] Exercise is also positively correlated with several quality of life domains, including physical and psychological well being,[23, 26] as well as decreased psychological distress, depression and anxiety.[22, 23]

In a study examining cancer patients who received high-dose chemotherapy (HDC) followed by autologous peripheral stem cell transplantation, 33 patients who participated in a supervised aerobic exercise program while hospitalized had a smaller reduction in physical performance at discharge -- measured as maximum speed on a treadmill stress test -- in comparison with 37 patients who did not join the exercise program.[20] The exercise program consisted of "biking" on a bed ergometer for 30 minutes daily (biking for one minute, resting for one minute), with daily pedaling frequency varying between 30-50 cycles/min. While both exercise and control groups experienced declines in physical performance, the patients who exercised had a 27% smaller decrease than the patients who did not exercise. In addition, the patients who exercised had a substantially shorter hospital stay (about 2 days shorter), a 13% shorter duration of neutropenia and thrombopenia, and a 20% lower pain severity, all of which were statistically significant. An interesting finding from this study was that there was no difference between the percentage of maximal predicted heart rate (220 minus age) reached by participants in both the training and control groups during the treadmill stress tests. This suggests that although the two groups performed differently during the treadmill tests, an equivalent amount of effort was expended.

That aerobic exercise seemed to ameliorate declines in physical function post-autologous BMT was mirrored in a more recent study by Dimeo and colleagues.[24] Patients participated in a daily treadmill walking aerobic exercise program while hospitalized, doing three-minute intervals at a speed equivalent to 70% of maximum heart rate, for a total of about 30 minutes.[24] At the end of seven weeks, even though hemoglobin concentration levels declined over the course of hospitalization (10.3 $\pm$ 2 g/dl baseline vs. 8.6 $\pm$ 0.4 g/dl at seven weeks), the patients' walking speed and rate of perceived exertion remained relatively unchanged.[24] However, it should be noted that only nine patients out of the original 66 patients remained hospitalized after seven weeks and thus were the only ones included in the data analysis for seventh week time frame.

Participation in a supervised in-patient aerobic exercise program also resulted in significant reductions in fear, anxiety and psychological distress in post-autologous PBSCT patients (n=27) compared to a non-training control group (n=32).[22] The exercise program utilized consisted of biking in supine with a bed ergometer for a total of 30 minutes per day, one minute of pedaling followed by one minute of rest, with pedaling rate ranging from 30-50 cycles/min. In contrast, reports of fatigue and somatic complaints increased significantly from baseline in the patients who did not participate in the exercise program. Dimeo and colleagues theorized that the improvement seen in psychological distress indicators in the patients who exercised are possibly explained by increased feelings of control or independence following improvements in physical performance, which in turn potentially translates into better social interaction, and thus a reduction in fear or anxiety.[22] They had observed anecdotally that the patients who participated in their study seemed to gain self-confidence over the course of the study. Another explanation of this improvement may be due to the nonspecific effects of human attention because the patients who exercised were asked to follow a structured exercise program with lots of contact or supervision by the study personnel. Conversely, the increase in fatigue symptoms in the patients who did not exercise could be due to greater requirements in effort and energy consumption when performing daily activities as a result of prolonged inactivity.

Even when participating in non-structured exercise, i.e., no set exercise program apart from physicians or nurses encouraging the patients to walk or use an in-unit bike ergometer, physical activity (specifically, duration of cycling and/or walking per day) during hospitalization was positively associated with QOL indices such as physical well-being, and negatively associated with depression, anxiety, fatigue, and days hospitalized.[23] Moreover, most of these correlations remained fairly strong after controlling for different medical variables (i.e., neutropenia, fever, mucositis).[23] These findings are remarkable given that the study participants (n=25) reported very low levels of exercise post-transplant, with 24% of the cohort not exercising at all, and with an average combined walking/cycling duration less than eight minutes per day. However, because of the observational nature of this particular study, it was not possible to fully establish that exercise caused an improvement in quality of life. It is possible, though, that exercise may have resulted in fewer medical complications which, in turn, manifested as improved quality of life.

An exercise program initiated during hospitalization and continuing after discharge from the hospital also yielded favorable results. Fourteen patients (ave. 30 ± 6 days post-BMT) who completed a six-week treadmill walking program achieved significant improvements in numerous physical performance parameters including walking speed, maximal training distance and intensity.[19] The treadmill program consisted of walking on a treadmill daily, with the duration initially set to three-minute bouts five times a day during the first week, progressing to 15-minute bouts twice a day later on, for a total duration of about 30 minutes. The participants seemed to embrace the exercise program, with about 90% of eligible patients ultimately participating in it. There were also anecdotal observations that the study participants seemed less depressed and more confident as their physical function improved; these observations were, however, not objectively assessed. The results from this study is interesting in that it suggests physical activity can be initiated safely early post-BMT and that significant improvements in physical function may be seen within weeks of discharge from the hospital, without apparent additional complications (e.g., episodes requiring hospitalization). In fact, a retrospective chart review of post-BMT patients participating in an exercise intervention suggests that improvements in function could be seen in as little as four weeks of intervention.[85] However, the chart review did not have a control group, which limits the interpretation of results. Also, there were a number of subjects who dropped out, but their reasons for doing so couldn't be ascertained because of the retrospective nature of the study.

In one of the earlier studies looking at exercise in post- BMT leukemia patients, Decker and colleagues had their patients cycle on an ergometer at least three times a week for at least 30 minutes.[86] They reported that exercise failed to significantly improve their patients' physical performance. Although there was long-term follow-up of patients (twelve months), the results from this study should be interpreted with caution, as there was a very small sample size; by the end of the study period, there were only five subjects left of the original twelve. Also, there could have been other complications that resulted in the patients not being able to exercise regularly. The patients were so debilitated that they were not able to start exercising until four months post-BMT. In spite of this, all of the patients reported a positive response to the exercise and felt it valuable during their treatment.

Most of the studies described above have examined in-patient exercise programs or exercise programs started soon after BMT/PBSCT, while the patient was still in the hospital. So far, there have been few studies looking at outpatient exercise programs, although there is evidence to suggest that a structured out-patient aerobic exercise program may be beneficial.[21] Using an exercise program consisting of walking on a treadmill six days a week for six weeks, post-stem cell transplant patients were able to improve physical fitness, improve maximal performance on a treadmill stress test, and demonstrate improved hemoglobin concentration. Exercise duration was gradually increased from 15 minutes a day to 30 minutes over the six weeks. By the end of the training period, the patients who exercised also reported that they were not as fatigued, and had fewer limitations, in usual activities such as stair climbing or shopping.

There is also empirical evidence that patients gain confidence and self-esteem as the exercise program progresses.[19] This could be interpreted as being part of the patient's response to increased physical functioning and independence, slowly gaining some control of their treatment and rehabilitation, rather than being passive participants.

There has been scant information on exercise and physical activity in patients following allogeneic BMT/PBSCT. This may be because of challenges in recruiting patients due to the complex nature of treatment, or because allogeneic transplants are done less frequently than autologous transplants. There has been only one study found to date that describes an exercise intervention with allogeneic BMT/PBSCT patients. Mello and colleagues reported on an exercise program that consisted of active range-of-motion exercises, stretching, and an interval treadmill walking regimen similar to one described by Dimeo,[19] with alternating periods of walking and rest, lasting a total of about 40 minutes.[84] An increase in muscle strength (measured through a strain-gauge dynamometer) of the large muscle groups in the shoulder, elbow, hip, knee and ankle was found in patients who exercised, compared to a control group who did not.[84] Both exercise and control groups exhibited a similar decrease in strength immediately after the transplant, but the mild to moderate intensity exercises performed by the exercise group appeared to be adequate to increase muscle strength to pre-BMT levels, while strength in the control group remained the same or declined. This study, however, only examined this single parameter and did not consider other, more functional parameters. It is interesting that the exercise program used in the study was mainly aerobic in nature, but no outcomes for cardiovascular function were measured.

All of the studies previously discussed have utilized aerobic-type exercises as the mode of exercise. Studies examining resistive exercises or mixed aerobic- resistive exercises have been few. A study that did use resistive exercises was published by Cunningham et al. examining patients on total parenteral nutrition post-BMT.[18] Although the main outcomes of interest were muscle physiology and nutrition indices, they nonetheless found that in-patients undergoing physical therapy five times a week, with 15 repetitions of biceps-triceps curls, bench presses, straight leg raises, sit-ups, etc., excreted less creatinine than the control group. The authors interpreted this result as demonstrating a muscle protein-sparing effect of exercise, based on the assumption that creatinine excretion is associated with muscle mass loss. These findings make physiologic sense, as resistance training has been shown to develop muscle strength, as well as increase endurance and mass, and improve mobility.[87] However, there were a number of limitations to this study -- there was substantial within-group variation, suboptimal nutritional support, and significant numbers of patients who had to drop out due to medical complications.

Thus far, only a single study has used a mixed aerobic, resistive exercise program following BMT/PBSCT transplantation. Hayes and colleagues followed post-autologous BMT/PBSCT patients from pre-treatment through approximately three to four months post-transplant.[26] These patients were assigned to a control or exercise group, where both groups met three times weekly over a three-month period, starting from about 14 to 21 days post-transplant, and were closely supervised by an exercise physiologist. The control group engaged in a stretching program consisting of about 20-30 stretches, with a 15 to 30 second duration for each stretch. The exercise group engaged in a moderate intensity, mixed aerobic-resistive exercise program which consisted of walking on a treadmill or riding a bicycle ergometer for 20-40 minutes, along with resistive exercises targeting large muscle groups using weight machines. At the end of the intervention period, both groups reported statistically significant improvements in overall quality of life scores from immediately post-transplant to three months post-transplant. However, the exercise group had greater improvements in overall quality of life (mean change of 17 $\pm$ 2.7 pts. vs. 4.5 $\pm$ 2.7 pts.). Moreover, significant improvements were seen in both the physical and psychosocial aspects of quality of life for the exercise group but not for the control group. The exercisers also reported fewer physical problems compared with the control group.[26] It should be noted, however, that each group in this study had only six participants, and although graded exercise testing was done on the participants to determine peak aerobic capacity, no between-group or within-group comparisons were done, even descriptively.

Several rehabilitation and BMT centers have started providing exercise and fatigue management programs to post-BMT/PBSCT patients, underscoring the emergence of exercise as an intervention to address the functional deficits following BMT/PBSCT. Dohnalek et al. described a recently established program at Georgetown University Medical Center that allows patients access to a 30-minute exercise session led by a physical therapist three times weekly.[88] These patients must be "fairly functional" and be cleared by the medical team for participation in the program. Results from preliminary data seem promising, with patients reporting that they enjoyed the exercises and socialization with other post-BMT patients. Cedars-Sinai Medical Center's Blood and Bone Marrow Transplantation Program instituted a twelve-week therapeutic exercise program along with a six-week fatigue management course.[89] Potential participants for their program are screened by a multidisciplinary team. Aside from exercises, this program also teaches energy conservation, time management, and lifeplanning skills. Outcome data is in the process of being collected. The University of Texas – M.D. Anderson Cancer Center, through its Rehabilitation Services Department, started its exercise program for outpatient post-BMT patients in 2001.[85] Patients receive individualized exercise programs, including aerobic and moderate resistance training on weight machines, three to five times a week, 45-60 minutes per session, depending on the patient's physical abilities. Scheduling of these patients is flexible to allow for blood work and administration of fluids, intravenous medications, and blood products that the patients receive on an outpatient basis. Preliminary data via retrospective chart review indicated significant gains in walking speed and endurance, as well as a reduction in fatigue severity at re-evaluation after a four-week period.[85] Moreover, no significant safety risks have been reported – while not all subjects who discontinued participation in the exercise program could be accounted for, atttrition for those accounted for has been mainly due to hospitalization secondary to medical complications, or to death.

Although research is strongly suggestive of a beneficial link between exercise and physical and psychological functioning in BMT/PBSCT patients, there are a number of limitations at present. Exercise interventions have been performed largely with autologous BMT/PBSCT patients only. Given the potentially devastating sequalae associated with allogeneic BMT/PBSCTs, assessing the effects of exercise training on this population is relevant. Most studies have shown exercise to be better than no intervention at all. In addition, researchers have mainly evaluated the effects of a supervised aerobic exercise program. In light of the increasing emphasis on self-management, and given the complex nature of cancer following BMT, there is a need to examine and compare different types of exercise regimens or conditions (i.e., supervised vs. unsupervised) in order to determine regimens that work best. As it has been hypothesized that there is possible muscle protein-sparing effect with resistance-type exercises,[18] examining an exercise program consisting of aerobic and resistance exercises would be beneficial.

Lastly, there is the lack of multidimensional outcome variables. Previous research has tended to focus almost totally on either objective physiologic outcomes (e.g., functional capacity, hematological indices) and/or psychological outcomes (e.g., depression, mood). Although these provide important information, they may not provide a complete picture of the changes resulting from exercise, given the complex nature of cancer following bone marrow transplantation. Although many post-BMT patients have difficulty with physical function or day-to-day task performance, directly observable, quantifiable, and functionally-based measures of physical performance, particularly in the context of cancer rehabilitation, is a relatively new development. Although measuring functional capacity through VO_2 max testing is still considered the gold standard,[90] many rehabilitation facilities may not have the necessary equipment for carrying out this testing. Moreover, the monitoring of patient participation in the intervention and of fluctuating symptoms such as fatigue and pain often requires frequent measurements to ensure accuracy. However, frequent measurements may be time-consuming and burdensome to the patient and may result in patient non-adherence to the intervention.

Adherence

In spite of the proven physical and psychological benefits of activity and exercise, many people have a difficult time initiating and adhering to an active lifestyle or to a structured exercise program. A majority of the adults in the United States have sedentary lifestyles and are not considering increasing their level of physical activity.[91-93] Studies have shown that approximately half of the people who attempt to embark on an exercise program revert to their previous activity levels within six months of initiating the exercise program.[94, 95, 93] It is reasonable to assume that adherence to a clinical prescription, e.g., an exercise program, will more likely result in a favorable outcome. However, the assumption cannot be made that improved adherence will result in the desired treatment goal, nor that non-adherence will result in failure. A variety of factors (personal, social and environmental) can affect treatment adherence and outcomes. Sherbourne et al.[96] noted that non-adherence at the beginning of a study was the strongest predictor of non-adherence two years later. In general, patients who were younger, not as worried about their health, or satisfied with their care were more likely to adhere to treatment recommendations.[96]

Self-efficacy, or how much confidence a person has to participate in physical activity under different constraints, has been found to be positively associated with consistent participation in exercise.[97] Courneya and Friedenrich found that exercise during cancer treatment was determined by intention, attitude and perceived behavioral control.[98] This finding suggests that patients who exercised, who had more active lifestyles, or had better physical functioning prior to cancer diagnosis would have favorable determinants to continuing or resuming exercise after cancer diagnosis. It has also been suggested that age might play a role in the degree of the patient's adherence to treatment, as older patients may have more difficulty than younger persons in understanding precisely the medical recommendations made to them; they also tend to be more passive recipients of care.[99] Understanding which factors contribute favorably to treatment adherence and outcomes is key to designing and tailoring effective exercise interventions for BMT patients.

In sedentary adults, people who received individually tailored feedback on physical activity engaged in significantly greater amounts of exercise and/or reached the Centers for Disease Control and American College of Sports Medicine (CDC/ACSM) guidelines for recommended minimum physical activity criteria over a six-month period, compared to those who received standard, printed self-help manuals.[100] Moreover, they were able to maintain their level of activity through a twelve-month follow-up.[101] The CDC/ACSM guidelines recommend at least 20 minutes of vigorous activity three times a week, or at least 30 minutes of moderate activity five times a week.[102] On the other hand, Bull and colleagues found that people who received tailored advice on exercise (verbal advice and a pamphlet created based on answers patients gave on a questionnaire) were significantly more active at one-month and six-month follow-ups, compared with a control group who received no instruction on exercise.[103] However, these researchers found no difference between participants who received tailored advice on exercise and those who received "standard" advice (verbal advice and a pre-printed pamphlet). An interesting result from this study was that as early as the one-month follow-up, less than 50% of all the participants were doing the recommended number of exercise sessions (ten sessions in two weeks).

Among older sedentary women (ages 45-60 years), higher retention rates were reported when they engaged in exercise that was supervised and center-based (i.e., at a community center) rather than home-based.[104] After six months, when the women who exercised in the community center were asked to exercise at home, their retention rates remained higher than those who had had home-based exercise programs since the beginning of the study. In the short term, at least, it appears that a combination of verbal advice and printed material and exercising in a center-based environment were useful in encouraging engagement in physical activity. Education on the key elements of exercise, such as exercise consistency, duration, percentage body fat; and motivation and monitoring participants' exercise progress, resulted in subjects being more likely to exercise at the recommended intensities.[105] Other studies have noted that patient education, along with regular feedback or reviews about the exercise program, appear to improve adherence.[106-108, 105] In an extensive review on the promotion of physical activity among women, Pinto and colleagues identified several perceived and actual barriers encountered by women when they engage in physical activity.[109] Some of the factors identified include lack of time, safety issues such as location of exercise facility, financial reasons, chronic physical health problems, work pressures, lack of exercise knowledge, lack of social support, and lack of guidance.[109] Women who had lower self-efficacy were also reported to be less likely to have optimistic attitudes about the benefits of exercise.[109]

Among patients with cancer, it appears that the patients' pre-morbid functional ability or exercise level was associated with the frequency and amount of exercise they would engage in.[10, 93] This is a finding that has been echoed in other studies on healthy cohorts.[110, 111] Many of the patients who reported not exercising were not previously active and had greater body mass indices, attributes which have been found to be good predictors of exercise adherence.[112]

Pinto et al. found that among breast cancer survivors, those who were inactive were usually older, had less social support from family and friends, and used fewer coping/adaptive strategies compared to women who exercised.[113] Some of the reasons that have been given by breast cancer patients and/or survivors for dropping out or discontinuing an exercise programs include scheduling problems, inertia, both cancer-related and other non-cancer physical problems that came up while the exercise program was ongoing, and being overwhelmed with their disease and its treatment.[114, 11, 93]

Studies in cancer patients have reported adherence or exercise completion rates ranging from 52% to over 90%.[75, 22, 10, 115, 116, 15] However, this is a parameter that is often unreported in many exercise studies with cancer patients, particularly when the patients are still undergoing treatment. In fact, it has been reported that during treatment, many patients manage to complete only about one exercise session per week, with only a low percentage of patients meeting the American College of Sports Medicine guidelines for recommended activity levels, despite knowing about the benefits of exercise.[117] Pickett and colleagues noted a "diffusion of treatment" effect among breast cancer patients during adjuvant treatment.[93] Although patients were randomized to either a usual care/control group or a usual care with exercise group, 52% of the usual care group (13/25) reported maintaining or increasing their exercise levels to at least moderate intensity level, while 33% of the exercise group (8/23) did not even start the exercise program or failed to exercise at the prescribed levels.[93] The authors theorized that this may have been due to the patients' trying to adopt healthier lifestyles as a result of their cancer diagnosis, or perhaps to their wanting to maintain pre-morbid exercise regimens.

A small majority of cancer patients and survivors have expressed a preference for unsupervised, self-paced exercise versus supervised, instructed exercise (57% vs. 43%).[117] Thus, it is not very surprising that relatively identical adherence rates were reported by patients who were on either a self-directed or supervised progressive walking program.[115] What is interesting is that although both of these groups had a greater increase in physical functioning compared with a control group, the self-directed group actually had a larger improvement in physical functioning than the supervised group.[115] These results could be due to the inclusion of many aspects thought to ensure effective home training, such as written guidelines for home exercise, education about exercise, and bi-weekly calls to check on their progress which, in turn, may have led these patients to exercise at higher intensities than the patients who were supervised.

Activity Measurement

In order for patients to gain maximal benefits from exercise, or any rehabilitation intervention for that matter, the prescribed exercises must be done. Thus, accurate means of monitoring and measuring exercise participation and other physical activity completed is essential. Clearly determining the effectiveness of an intervention is confounded if the intervention is not completed as directed. A way to ascertain patient adherence is to monitor the patient frequently. However, frequent monitoring may be intrusive and time-consuming. One method that has been generating interest of late as a direct, non-invasive, long-term indicator of activity is the use of activity monitors, or actigraphs. An actigraph is a small, wrist- or belt-worn device, typically about the size of a large wristwatch. It measures movement through a rate-sensitive piezo accelerometer that senses motion in three planes as accelerations within the threshold of normal motion of human beings.[118, 119] Thus, higher levels of activity intensity would be accompanied by greater frequency and duration of movement. Currently, most actigraphs in the market are able to collect and store data for up to three months, and the data can be displayed graphically and summarized through a computer interface. Historically, the actigraph has been used to provide objective data for sleep disorders. However, recently they have begun to be used for the assessment of rest and movement patterns in conditions such as attention deficit hyperactivity disorders, fibromyalgia, Alzheimer's disease, post-surgery, and cancer.

Actigraphs provide an objective means of quantifying both quality and quantity of sleep and movement. They can distinguish between physical and sedentary activity.[120] A high correlation (r =.81) has been reported between self-reported physical activity and activity duration as measured by the actigraph (time-above-threshold counts).[121] Significant correlations were also found between actigraph counts and oxygen uptake and heart rate during more vigorous and sedentary activities.[120] Actigraph algorithms characterizing sleep have been found to provide reliable approximations of total sleep time (r = .77), percent sleep (r = .82), sleep efficiency (r = .71), sleep latency (r = .90), and wake time after sleep onset (r = .63).[122]

The use of actigraphs in oncology patients is currently not very widespread, with almost all published studies occurring in the past ten years.

Miaskowski and Lee, using wrist actigraphs to monitor the activities of outpatients undergoing radiation therapy over a 48-hour period, reported that the actigraphs were valid and objective measures of sleep efficiency in this population.[123] Activity monitors were also found to be reliable in measuring total physical activity (ICC = 0.65 - 0.91) and had adequate association with other measures of functional status.[124] Actigraphs have been used as an adjunct to patient diaries in the determination of sleep and wake cycles. Comparative estimates of total sleep and wake times, as well as relatively high rates of compliance, have been shown for both methods of measurement.[125-127] In fact, Eissa and colleagues found that wearing the wrist actigraph had a higher compliance rate than diary completion (90% vs. 71%, respectively).[127] It has been suggested that recording for five consecutive days provides a reliable estimate of mean 24-hour movement for a subject and is optimal to reach an 80% reliability in measuring physical activity.[128, 129]

Previous studies using actigraphs have shown fluctuating patterns of lowered activity and disturbed sleep in cancer patients receiving treatment, as well as those who had recently completed treatment.[130, 131, 15] Young-McCaughan and colleagues reported their cohort of cancer patients had average sleep episodes that lasted about 48.5 minutes, awakening an average of 14 times per night.[15] Irregular sleep patterns were also associated with higher fatigue levels, greater symptom distress, and poorer physical and social health status.[130] Disturbances in rest/activity rhythms were also linked with lower functional scores and higher symptom scores on quality of life questionnaires.[132] One finding of note is that fatigue levels decreased as activity increased,[131] supporting other studies on the benefits of exercise during cancer. However, there is no quantitative information regarding baseline activity levels in the BMT population. Moreover, whether BMT patients exhibit similar irregular patterns of activity, particularly if they are engaged in an exercise intervention, has not been addressed.

It appears that actigraphy may provide a relatively simple, reliable means of evaluating rest and activity patterns in cancer patients. Because the monitoring of the activity is non-invasive, there are few restrictions on its use, particularly in an outpatient setting. The actigraph is able to quantify both the amount and intensity of physical activity of patients during an extended period of time in their own environment. However, there are some limitations. Actigraphs typically use rate-sensitive accelerometers and record the rate of change of a movement, not the displacement. Thus it would not be able to differentiate between a loaded versus an unloaded activity, or between similar activities of differing difficulty level (e.g., walking uphill versus walking on level ground). Attempts to address this particular limitation have been made through removal of the proof mass from the piezo accelerometer, resulting in an increase in Proportional Integrating Mode (PIM – a measure of activity intensity) range, thus allowing a better representation of rate-derived daytime activities.[133] Additional testing is ongoing in this area. Another limitation is the relatively small sample sizes (ranging from 7 to 24) used in oncology actigraphy studies done so far. However, the findings do suggest that there is a relationship between lower levels of activity, disturbed sleep, fatigue and decreased quality of life in cancer patients. Actigraphs seem to be a promising complement to other methods of measuring movement and activity such as self-report questionnaires or physiologic measures.

Clinical Assessment of Function

Traditionally, clinical assessments of functional ability have often been inferred from physiologic measures or self-report scales or questionnaires. These methods are used to monitor the patient's progress and/or serve as outcome measures regarding treatment. Unfortunately, these indicators may not adequately quantify physical function. Physiologic measures (e.g., graded exercise tests, hematological indices) are often narrowly defined and may be time-intensive or require special equipment to measure. They are also often not reflective of the actual tasks that patients have to accomplish on a regular basis. Self-reports, on the other hand, can be subject to personal biases or inaccurate recall. For example, adults tend to overestimate recalled or self-reported activity intensity, particularly of moderate activity (≈ 4 metabolic equivalents (METs)).[134] Moreover, depending upon the way a question is phrased and the manner in which it must be answered, self-reports may not differentiate between whether a physical activity is not done by choice or by inability; whether it is done but done differently; or done inefficiently and is therefore burdensome in terms of effort.

Recently, a standardized physical performance test battery for measuring physical function in patients with cancer was tested and validated.[135] The test battery consists of tasks that are fundamental to day-to-day activity, tests fine and gross motor function and challenges speed, endurance, and balance. The timed tests included picking up coins, reaching up, putting on a sock, standing from sitting, walking 50 feet. For distance, tests were a forward reach activity and a 6-minute walk. Inter-rater and test-retest reliabilities were good to excellent (ICC or *r* values >.8) and face, discriminate and construct validities were established.[135] The results of this study showed patients with cancer to be significantly restricted in their physical function, with control subjects outperforming patients with cancer by a factor of 2 to 4, depending on the specific test. Thus, the use of physical performance tests holds potential as an assessment and outcome measure for testing a variety of different treatment interventions for patients with functional deficits. They also serve as valuable complements to other methods of assessment and outcome measurement.

Several questions should be explored that will contribute to this growing body of evidence supporting exercise training as a useful intervention following BMT/PBSCT: What type of exercise (supervised vs. unsupervised) is most effective for this population? How does fatigue level, activity level, and quality of life change as a result of supervised versus unsupervised exercise? Is there a way to identify or characterize who best benefits from either of these two types of exercise?

CHAPTER III

EXERCISE IN CANCER PATIENTS AFTER RECENT ALLOGENEIC BONE MARROW TRANSPLANTATION: A PRELIMINARY ANALYSIS OF PHYSICAL PERFORMANCE, SYMPTOM SEVERITY AND QUALITY OF LIFE

Abstract

The purpose of this investigation was to perform an interim, exploratory examination describing the effect of short-term clinician-directed and self-directed exercise programs in recent allogeneic bone marrow transplant patients in terms of multi-dimensional outcomes. These multi-dimensional outcomes comprise clinician-measured physical performance tests, and patient self-reports. A second purpose was to determine the relationship of physical performance on self-reported pre-treatment measures. Forty-four (44) patients (26 males and 18 females, ages 22 – 71 years) with a primary cancer diagnosis of lymphoma or leukemia, within 6 months of an allogeneic bone marrow transplant/ peripheral blood stem cell transplant (BMT/PBSCT) served as subjects. They were randomly assigned to a self-directed non-supervised or a clinician-directed supervised exercise group. The self-directed group received instruction on a home exercise program and walking regimen. The supervised group performed mixed aerobic-resistive exercises for 45-60 min., thrice a week for 4 weeks. Subjects were evaluated at baseline, 4 and 8 weeks using a physical performance battery, Brief Fatigue

Inventory, M.D. Anderson Symptom Inventory, and Functional Assessment of Cancer Therapy – Bone Marrow Transplant (FACT-BMT). Because of low subject numbers and insignificant observed power for group differences, the exercise groups were combined into one group for data analysis. Both groups showed improvements after 4 weeks in walking speed, endurance and strength. These improvements were maintained after 8 weeks despite reported increases in BMT-specific symptom severity. Declines in fatigue severity and increased scores in overall quality of life and physical and functional well being were noted at both the 4 and 8 week follow-up compared with baseline. Overall quality of life, physical and functional well being were significantly associated with fatigue and BMT-specific symptom severity. Within the time period measured in this study, preliminary results suggest that both clinician-directed and self-directed exercise regimens are beneficial for post-allogeneic transplant patients. Significant relationships noted among self-reported measures point to the possible influence of fatigue and/or BMT-related symptomatology on quality of life, particularly its physical and functional aspects.

Introduction

As of 2005, an estimated 55,000 bone marrow/ peripheral stem cell transplants (BMT/PBSCT) are performed every year worldwide, with a growth rate of about 10- 15% per year.[1] These procedures are regarded as optimal treatment for many hematological cancers such as leukemias and lymphomas. However, despite the good clinical results and longer survival rates associated with BMT/PBSCTs, various physiological and psychological transplant-related sequalae may occur that limit patients function and activities.[35, 44, 40]

Many patients who undergo bone marrow transplantation will have already undergone previous regimens of chemotherapy and/or radiation therapy, and thus may have already existing declines in function.[58, 59, 35] In addition, bone marrow ablation results in cytopenias, with its associated concerns of developing anemia and infections. Fatigue, loss of physical performance, and decreased strength have been cited as common symptoms associated with BMT/PBSCT.[51, 49, 50, 7, 84] Other reported problems include: reduced cardiopulmonary functional capacity, difficulty sleeping, dyspnea, nausea, increased anxiety, depression, psychological distress and compromised quality of life (QOL) relative to premorbid status.[51, 53, 52, 54-56, 61]

Transplant-related consequences are particularly marked in patients undergoing allogeneic BMTs.[2, 38, 3, 136, 4] Aside from the side effects common to all transplant recipients, allogeneic transplant recipients also run the risk of contracting graft-versus-host-disease (GVHD), a potentially devastating complication of allogeneic bone marrow and stem cell transplants wherein the patient's immune system rejects the new bone marrow and effectively destroys it. GVHD has been found to result in long-term impairments in physical, role and social functioning.[137] Additionally, patients receiving allogeneic transplants are prone to infections because of neutropenia and/or prophylactic immunosuppressive therapy given to prevent GVHD.[44]

Many of the sequalae experienced by post-bone marrow transplant patients appear to be attenuated or alleviated through regular exercise. Among patients following autologous bone marrow transplantation, participation in exercise has been shown to improve walking speed and distance,[19-21] increase total energy expenditure and skeletal mass,[25] boost hemoglobin concentration,[22] improve quality of life,[26] reduce fatigue severity,[21, 22] decrease duration of neutropenia,[20] psychologic distress,[22] length of hospitalization,[20] and reduce muscle mass loss.[18] Exercise is also significantly correlated with several quality of life domains, including physical and psychological well being, depression and anxiety, [23, 26] even after controlling for several demographic and medical variables.[23, 26]

In contrast, among patients following allogeneic transplantation, there is a scarcity of empirical data regarding the effect of exercise on activity levels and symptom severity, particularly after discharge from the hospital. Mello and colleagues report improvements in the strength of large muscle groups of post-allogeneic bone marrow transplant patients who participated in mild to moderate intensity exercises compared to a non-exercising control group.[84] However, the exercise program was initiated as an in-patient program, and did not evaluate other parameters, save for muscle strength. Previous studies on post-BMT patients have mainly utilized supervised exercise programs. In light of the increasing emphasis on self-management, and given the complex nature of cancer following BMT, there is a need to examine and compare different types of exercise regimens or conditions (i.e., supervised vs. unsupervised), as well as to determine demographic or clinical variables that may impact patients response to exercise. Currently, a multi-disciplinary team at the University of Texas – M.D. Anderson Cancer Center is conducting a randomized trial investigating the longitudinal effects of different outpatient exercise regimens on patients who have undergone recent allogeneic BMT/PBSCT.[138] This study is still in the process of data collection as of this writing. Therefore, the purpose of this study was to perform an interim, exploratory examination and describe the effect of short-term clinician-directed, supervised and self-directed, non-supervised exercise programs in terms of multi-dimensional outcomes. These multi-dimensional outcomes comprise clinician-measured physical performance tests and patient self-reports. A second purpose was to determine the relationship of physical performance and self-reported pre-treatment measures.

Methods

Subjects

Forty-four (44) patients (26 males and 18 females, ages 22 – 71 years) participated. The subjects were recruited from the Bone Marrow Transplant Service, through the BMT clinic, Ambulatory Treatment Center (ATC), and the Department of Rehabilitation Services of the University of Texas – M.D. Anderson Cancer Center. These subjects were part of a larger series of studies examining outpatient rehabilitation interventions on the quality of life in patients following recent allogeneic bone marrow/ peripheral stem cell transplantation. To be eligible, the subjects had to be more than 17 years in age, have a primary diagnosis of lymphoma or leukemia, be less than 6 months post-allogeneic bone marrow/peripheral blood stem cell transplant, be referred for physical therapy, and be able to speak or understand English. Subjects were all ambulatory, and were able to perform most self-care activities independently, requiring no more than moderate assistance (no more than 50% assistance). Every effort was made to recruit from both genders and from different racial and ethnic backgrounds. All subjects signed informed consent forms approved by the institutional review boards of the University of Texas – M.D. Anderson Cancer Center, Houston, TX, and Texas Woman's University, Houston, TX.

Procedure

Subjects were randomly assigned, through the Patient Management Data System (PDMS), to a clinician-directed supervised exercise group (n=22) or to a self-directed, self-paced, unsupervised exercise group (n=22). Subjects in the self-directed exercise group received instruction on a Home Exercise Program according to the current standard of care for post-BMT patients at M.D. Anderson Cancer Center. This standard of care consists of a multi-disciplinary educational session where patients receive instruction from nurses, social workers and physical therapists or physical therapist assistants. The physical therapist or assistant educates the patients on home exercises consisting mainly of a walking regimen. Patients also received education on the importance of staying active through general physical activity (i.e., walking) and performing as much of one's activities of daily living is emphasized. They were also instructed about steroid myopathy and peripheral neuropathy; exercise safety; and infection control considerations.

Subjects in the clinician-directed exercise group participated in a supervised, structured exercise program. This exercise program was conducted in the Rehabilitation Services gym, and was tailored to the patient's needs and included aerobic exercises, resistive exercises (free weights and machines), and walking on a treadmill or biking on an ergometer. Each exercise session lasted approximately 45-60 minutes, thrice a week, with at least 20 – 30 minutes comprising aerobic exercises and the rest of the time comprising resistance exercises. The sessions were scheduled to coincide with the patient's scheduled visits to the hospital for intravenous fluids or medical follow-up. This was done to encourage the patients to attend the exercise sessions, as they would not have to schedule a special trip to the facility. The entire exercise program lasted four weeks. Subjects who were in the self-directed exercise group were offered the opportunity to take part in a clinician-directed exercise program at the end point of the study.

Demographic information and patient self-efficacy (i.e., the patients' confidence in their ability to carry out the exercises), was obtained during baseline evaluation. Patients were evaluated upon entering the study (baseline), at the end of the exercise sessions (4 weeks) and 4 weeks after the end of the exercise intervention, or 8 weeks post-baseline. All subjects were evaluated using the physical performance battery and Brief Fatigue Inventory (BFI), M.D. Anderson Symptom Inventory (MDASI), and Functional Assessment of Cancer Therapy – Bone Marrow Transplant (FACT-BMT). Global perception of change was obtained at the end of weeks four and eight. Participants were contacted by telephone or visited at the ATC to remind them of follow-up evaluations.

Measures

Physical performance measures

The physical performance test battery (PPT) consists of a set of tasks where the time taken to complete the task or the distance reached is measured. Simmonds established the reliability, validity and clinical usefulness of this battery in patients with cancer.[135] There was excellent test-retest reliability ($r \geq 0.8$), all tasks had face validity, and they proved acceptable to the patients. In addition, the battery was found to be moderately responsive to change and a better predictor of disability than either impairment or psychosocial measures alone.[135] The testing order of the performance tasks was done randomly, except for the 6-minute walk, which was always performed last.

- *6 minute walk*. Subjects walked as far, as fast and as safely as they could for six minutes while pushing a measuring wheel. The distance walked was then measured and recorded.
- *50-foot walk at patient's fastest speed.* Subjects were timed as they walked a distance of 50 feet. They were told to walk as fast and as safely as they could.
- *Forward reach*. Subjects stood next to a wall on which a meter stick had been mounted horizontally at shoulder height. The subjects stood next to the meter stick with their shoulder forward

flexed to 90, elbows extended, wrist at neutral and fingers extended. Keeping their heels on the floor, patients reached forward along the meter stick as far as they could. The distance reached was then measured and recorded in centimeters.

- *Timed repeated sit-to-stand.* Subjects sat on a flat surface, 18 inches in height. They were asked to rise to a standing position, without using their arms to push off, and return to a sitting position, as quickly and as safely as possible, twice.

Self-report measures

The Brief Fatigue Inventory (BFI), which assesses fatigue severity, and characterizes the impact of fatigue on function; its reliability and validity have been established in patients with cancer.[139] It consists of 9 items measured on a numeric scale from 0-10, with 0 being "no fatigue", or "fatigue does not interfere" and 10 being "fatigue as bad as you can imagine", or "fatigue completely interferes". Higher scores indicate higher levels of fatigue and greater interference of fatigue with life. The BFI items used for this study were "worst level of fatigue in the last week", the total BFI interference score, which is the mean score of the 6 items on the BFI that assess the amount that fatigue has interfered with different aspects of the patient's life (e.g., general activity, mood, walking ability, normal work, relations with other people, enjoyment of life), and the total BFI score, which is the mean score of all 9 items of the BFI.

The M.D. Anderson Symptom Inventory – BMT (MDASI-BMT), a brief measure of the severity and impact of cancer-related symptoms. The core MDASI measures 13 cancer-related symptoms and 6 items describing how much symptoms interfered with different aspects of the patient's life in the last 24 hours. Both the symptom scales and symptom interference scales of the MDASI exhibited high internal consistency ($\alpha \geq .82$).[140] The BMT module contains the core MDASI items plus 6 additional symptoms identified as problem areas by transplantation physicians and nurses. Higher scores indicate higher levels of symptom severity or interference of treatment-related symptoms with life. The MDASI-BMT items used were the BMT subset severity scores (the mean of the 6 BMT subset items), the total severity score (the mean of the 19 symptom severity items) and total interference scores (mean of 6 items that assess how much treatment-related symptoms have interfered with the patients' life).

The Functional Assessment of Cancer Therapy – Bone Marrow Transplant (FACT-BMT) measures quality of life in bone marrow transplant patients. The FACT –BMT (version 4) is composed of the FACT – General, that addresses general health-related quality of life for cancer patients, with the addition of a 23-item Bone Marrow Transplant subscale (BMTS), that addresses issues specific to bone marrow transplant patients. Each item on the FACT-BMT consists of a 5-point categorical scale, with answers ranging from 0 (not at all) to 4 (very much), that applies to the previous seven days. It provides a total score for overall quality of life and subscale scores. Coefficients of reliability and validity ranged from 0.86 to 0.89 for the entire FACT-BMT and 0.54 to 0.63 for the BMTS. The BMTS was able to discriminate patients on the basis of performance status rating and also demonstrated sensitivity to change over time.[141] A higher score corresponds with a higher quality of life. A global QOL score and five subscale (physical well being, social well being, emotional well being, functional well being and BMT) scores were calculated for this study.

The self-efficacy scale is a measure that taps into subjects' perceived capabilities to exercise over a specified period of time in the face of commonly identified barriers to participation. Participants indicate their degree of confidence for each item on a 0% (no confidence at all) to 100% (completely confident) scale. The confidence scores are then summed and divided by the total number of items giving a possible range of 0 – 100% -- a higher number indicating a greater degree of confidence. This measure was obtained during baseline evaluation.

Global perception of change is a one-item question that seeks the patient's perception of change in his or her overall condition since the beginning of the study period. It consists of a numerical scale on perceived magnitude of change and perceived importance of change. The higher the score, the larger the magnitude of change or the more important the change. A negative score indicates that the patients believed that their condition had gotten worse, or that the change in their condition was unimportant. Scores ranged from -7 to 7. This measure was obtained at the end of four and eight weeks.

Statistical analysis

Data were analyzed using SPSS version 11.5 (SPSS, Chicago, IL) for Windows software (Microsoft Corp., Redmond, WA). Descriptive statistics (mean, standard deviation) were computed on all variables for each group: clinician-directed exercise and self-directed exercise. Statistical tests of significance (i.e., two-way MANOVA) were not performed as data collection on the main, larger study was still ongoing at the time of this analysis, and the study collaborators did not want to compromise the alpha significance level. Pearson product moment correlations were used to examine the relationships between the physical performance measures and self-reported measures. Stepwise regression analyses were performed on demographic variables and self-report to determine significant predictors of physical performance. An alpha level of $p \leq 0.05$ was selected.

Results

Demographic data of the subjects are presented in Table 1. No significant differences were found between the groups. Majority of the subjects were male, Caucasian, and had a primary cancer diagnosis of leukemia. Subjects were 14 to 63 days post-allogeneic bone marrow transplantation, with slightly more subjects receiving donor bone marrow than peripheral blood/stem cells (n= 24 and 20, respectively).

Table 1. Subject characteristics (mean ± SD)

	Clinician-directed Exercise	Self-directed Exercise
n	22	22
Age (years)	44.95 ± 13.58	51.63 ± 11.10
Gender		
Male	13	13
Female	9	9
Ethnicity		
Caucasian	19	17
Hispanic	3	2
African American		1
Asian American		2
Type of cancer		
Leukemia	13	15
Lymphoma	9	7
Source of BMT		
Bone marrow	10	14
Peripheral blood/stem cells	12	8
Age at BMT (years)	43.68 ± 13.30	50.36 ± 11.26
Time since BMT (days)	31.64 ± 13.90	28.84 ± 11.32

A little over half (24/44, 54%) of our cohort reported that they often or always exercised prior to their BMT/PBSCT. Thirty four percent (15/44) reported that they seldom exercised and 11.4% (5/44) claimed that they never exercised prior to their BMT/PBSCT. Majority of the subjects (29/44) expressed confidence that they would be able to exercise at least three times a week. The data reported in Table 2 show that our subjects expressed a wide range of confidence with regards to their ability to exercise in the face of barriers to exercise. Relatively similar degrees of confidence in the face of several barriers to exercise were noted in both groups. In general, subjects expressed the least level of confidence about being able to exercise when they were tired or when they had no time. High levels of confidence were reported regarding intention to exercise at least thrice a week; subjects in both groups stated that they intended to exercise about 4 days a week.

Table 2. Patient self-efficacy

	Clinician-directed exercise	Self-directed exercise	Total
Able to exercise when tired (0-100%)	60.83 ± 26.47	54.71 ± 26.72	57.86 ± 26.38
Able to exercise when no time (0-100%)	57.22 ± 27.40	59.71 ± 31.45	58.43 ± 29.02
Able to exercise when bad mood (0-100%)	74.72 ± 29.73	70.88 ± 27.96	72.86 ± 28.52
Able to exercise specified duration (0-100%)	85.53 ± 16.17	88.82 ± 11.53	87.14 ± 14.00
Able to follow instructions (0-100%)	96.28 ± 6.77	95.00 ± 8.66	95.66 ± 7.66
Able to exercise 3x/week (0-100%)	88.89 ± 12.78	89.41 ± 19.11	89.14 ± 15.93
Able to overcome obstacles (0-100%)	85.56 ± 17.90	87.94 ± 18.96	86.71 ± 18.19
Intention to exercise (days)	4.89 ± .32	4.71 ± .59	4.80 ± .47

Means and standard deviations of the subjects' physical performance over time are shown in Table 3. Four subjects (2 from the clinician-directed group and 2 from the self-directed group) had missing physical performance data and so were not included in the baseline analyses. Overall, both groups showed steady improvements from baseline to 8 weeks in the 50-foot walk, 6-minute walk, and repeated sit to stand. Functional reach remained relatively unchanged for both groups. Subjects who were in the clinician-directed exercise group and self-directed exercise group generally walked faster, farther and were performed the sit to stand task faster after 8 weeks compared to baseline. In general, the supervised group had a greater improvement in the physical performance tests from baseline to 4 weeks, as well as from 4 weeks to 8 weeks, with the exception of the 6-minute walk, where there was a slight decline from the 4-week to 8-week distance. Line graphs comparing the 2 groups in each of the performance tests are shown in Figures 1-3. At the end of 8 weeks, subjects in the clinician-directed exercise group had improved their walking speed by about 18% and their walking distance by about 17% compared to baseline. Sit to stand time was 32.5% faster than baseline. Improvements in walking speed, walking distance, and sit to stand in the self-directed group were 14%, 22% and 21%, respectively.

Table 3. Physical performance measures (mean ± SD) for clinician-directed and self-directed exercise groups

	Clinician-directed			**Self-directed**		
	Baseline	4 weeks	8 weeks	Baseline	4 weeks	8 weeks
n	20	13	10	20	14	8
50 foot walk (sec.)	9.41 ± 1.46	8.46 ± 1.60	7.76 ± 1.26	9.39 ± 1.71	9.12 ± 1.56	8.08 ± 1.26
6 min. walk (m.)	423.14 ± 113.50	500.43 ± 108.69	493.71 ± 232.09	411.35 ± 74.88	464.16 ± 66.31	502.23 ± 44.54
Sit to stand (sec.)	4.09 ± 1.45	3.29 ± .77	2.76 ± 1.03	4.25 ± 1.39	3.49 ± 1.34	3.34 ± 1.49
Functional reach (cm.)	34.00 ± 8.24	34.69 ± 4.94	34.00 ± 12.20	36.36 ± 5.47	37.10 ± 5.76	37.00 ± 5.87

Figure 1. Improvements in time to walk 50 feet for clinician-directed and self-directed groups over 8 weeks.

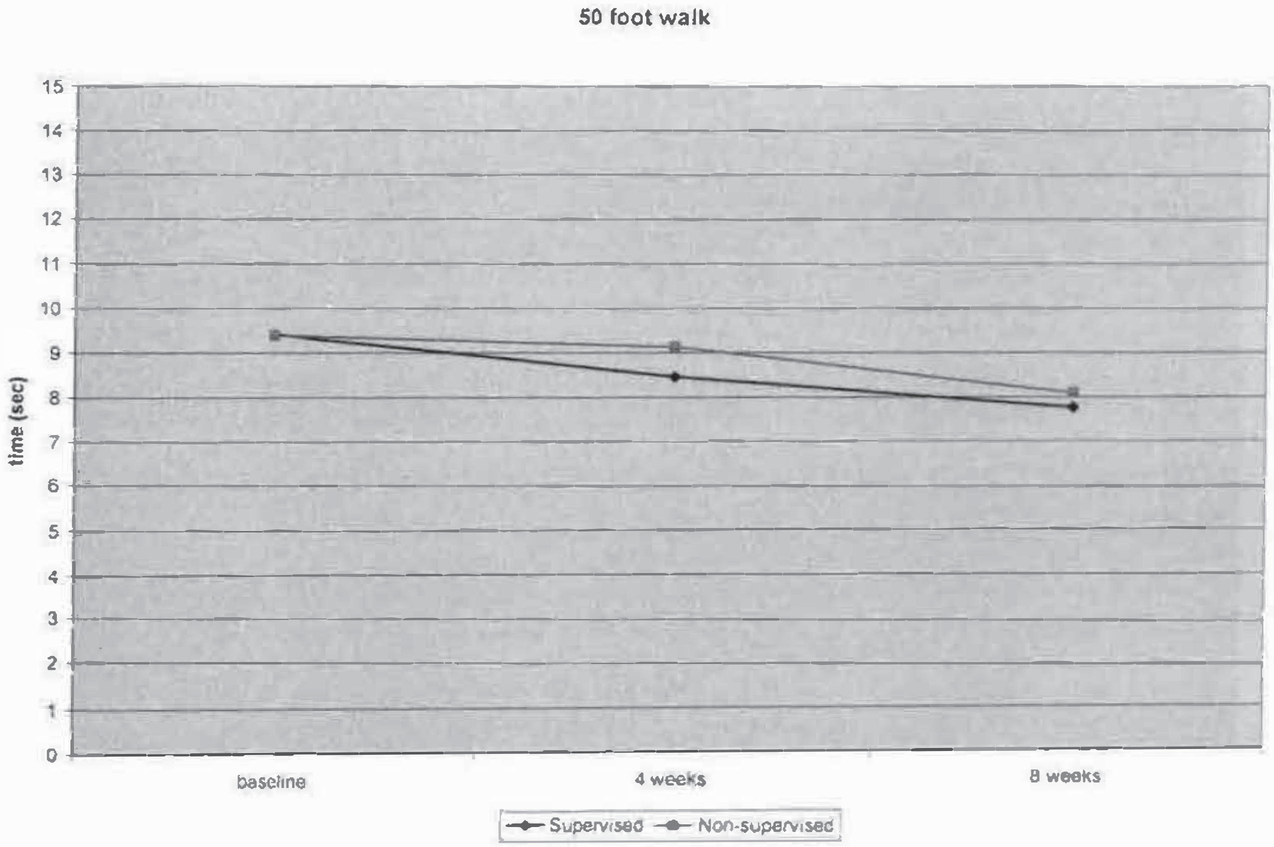


Figure 2. Improvements in distance walked in 6 minutes for clinician-directed and self-directed groups over 8 weeks.

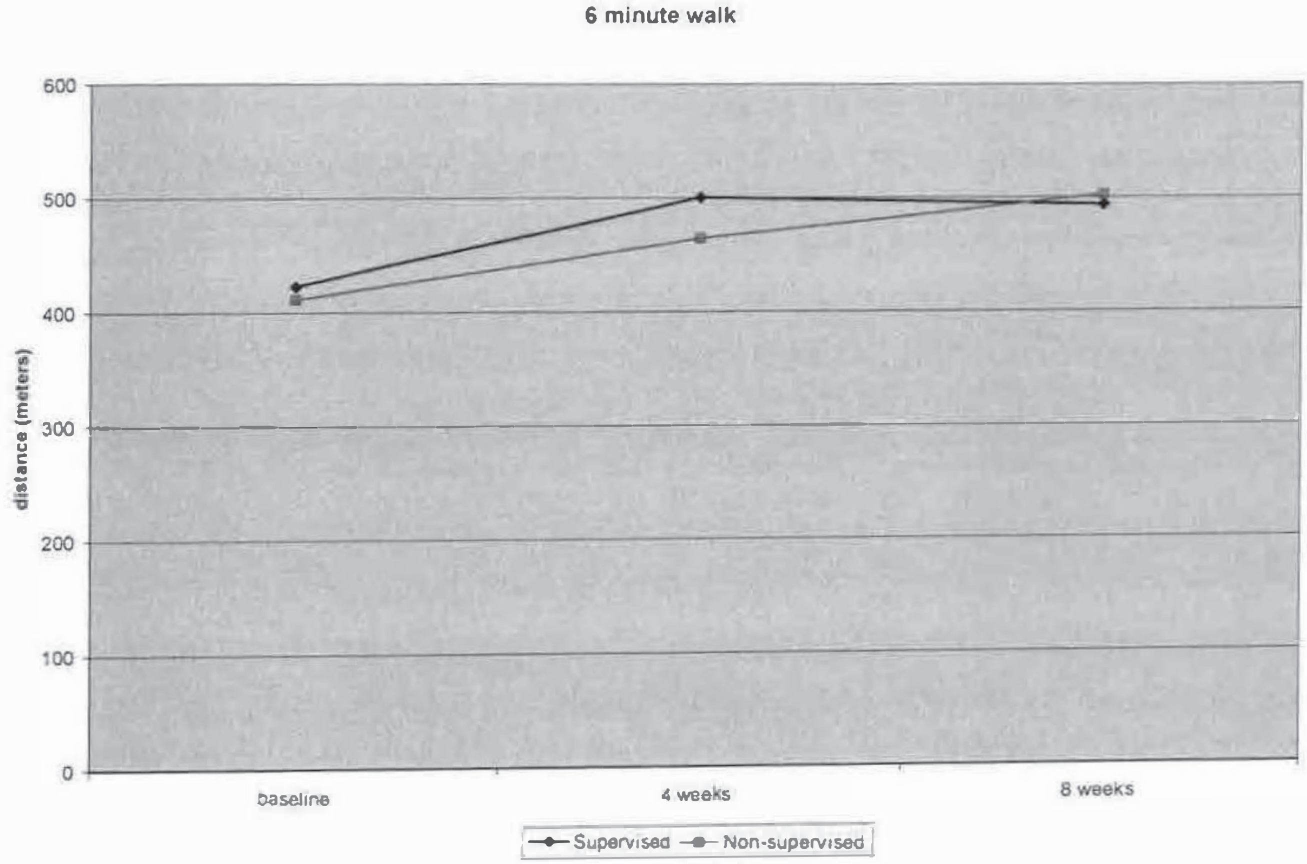
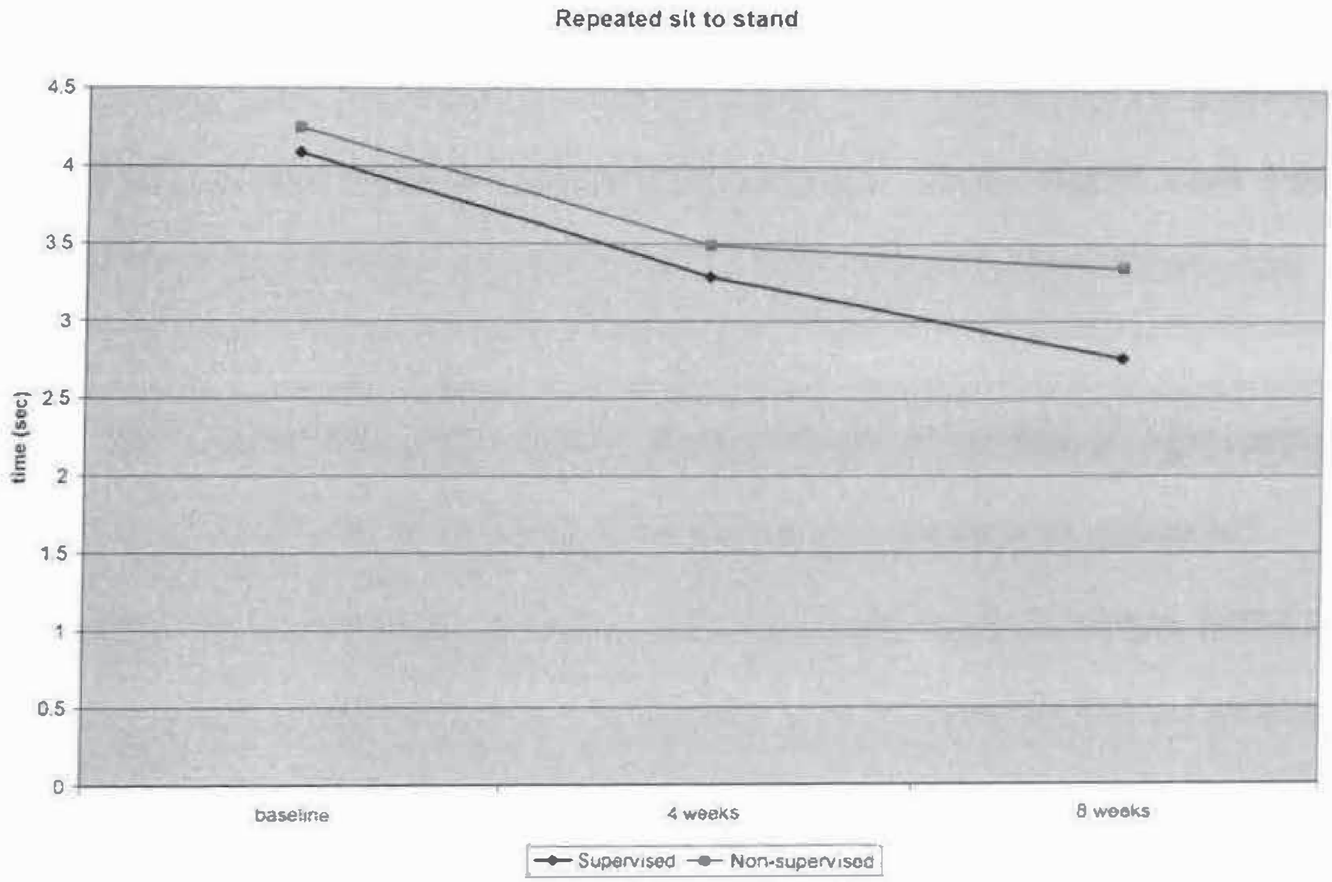


Figure 3. Improvements in time to complete sit to stand for clinician-directed and self-directed groups over 8 weeks.



There were a number of participants who were not able to complete the study. At the fourth week follow-up, twelve subjects had BMT-related complications that necessitated hospitalization and thus were forced to drop out of the study, two subjects passed away, one withdrew on his physician's advice, and two withdrew due to other reasons. By the eighth week follow-up, three subjects were hospitalized for BMT-related complications, two passed away, and four were lost to follow-up.

Because of the small number of subjects left at the end of eight weeks and inconsequential power observed for the sample (computed power for differences between group was < .2 for the physical performance tests), the two exercise groups were combined into a single group for the succeeding analyses.

The physical performance tests over time for the combined groups are shown in Table 4. Improvements ranging from a small 3.15% in the functional reach to an encouraging 27.34% in the repeated sit to stand were observed in all of the physical performance measures. Generally, these changes were larger between baseline and 4 weeks compared to changes between 4 and 8 weeks. When results of the baseline physical performance tests were plotted onto a scatterplot, no obvious cut-off points were noted. However, subtle changes in the slope of the line were noted in 2 places for most of the tests. Hence, tertile norms were calculated. Scatterplots of the change scores for selected physical performance tests from baseline to 4 weeks, and from baseline to 8 weeks are presented in Figures 4 – 9. Tertile percentile norms for the physical performance tests are outlined in Table 5.

Table 4. Physical performance tests for combined exercise group (means ± SD)

	Baseline	4 weeks	8 weeks	Overall % change
n	40	27	18	
50 foot walk (sec.)	9.40 ± 1.57	8.81 ± 1.58	7.77 ± 1.08	+ 17.34%
6 min. walk (m.)	417.89 ± 94.53	481.85 ± 88.63	506.63 ± 167.53	+ 21.23%
Sit to stand (sec.)	4.17 ± 1.40	3.40 ± 1.10	3.03 ± 1.25	+ 27.34%
Functional reach (cm.)	35.25 ± 6.91	35.99 ± 5.43	36.36 ± 9.80	+ 3.15%

Table 5. Percentile norms for physical performance tests for combined exercise group

	Percentile 33	Percentile 66
BASELINE (n = 40)		
50 foot walk (sec.)	8.83	9.84
6 min. walk (m.)	365.24	450.78
Sit to stand (sec.)	3.43	6.70
Functional reach (cm.)	33.77	36.00
4 weeks (n = 27)		
50 foot walk (sec.)	8.38	8.96
6 min. walk (m.)	444.14	501.30
Sit to stand (sec.)	2.75	3.58
Functional reach (cm.)	33.00	39.48
8 weeks (n=18)		
50 foot walk (sec.)	7.81	8.24
6 min. walk (m.)	492.75	555.26
Sit to stand (sec.)	2.28	3.30
Functional reach (cm.)	37.50	40.10

Figure 4. Change in time from baseline to 4 weeks, repeated sit to stand

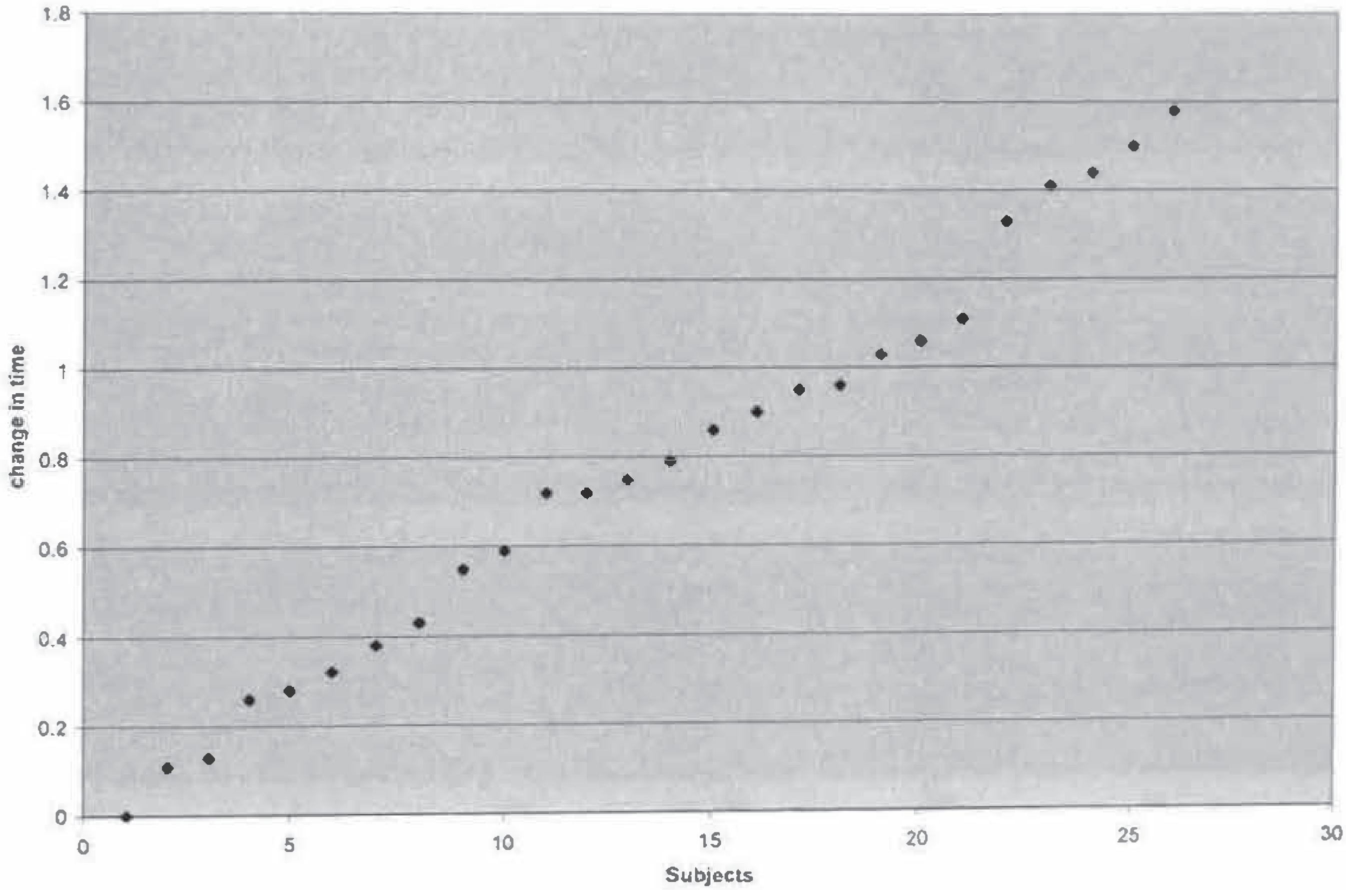


Figure 5. Change in time from baseline to 4 weeks, 50 foot walk

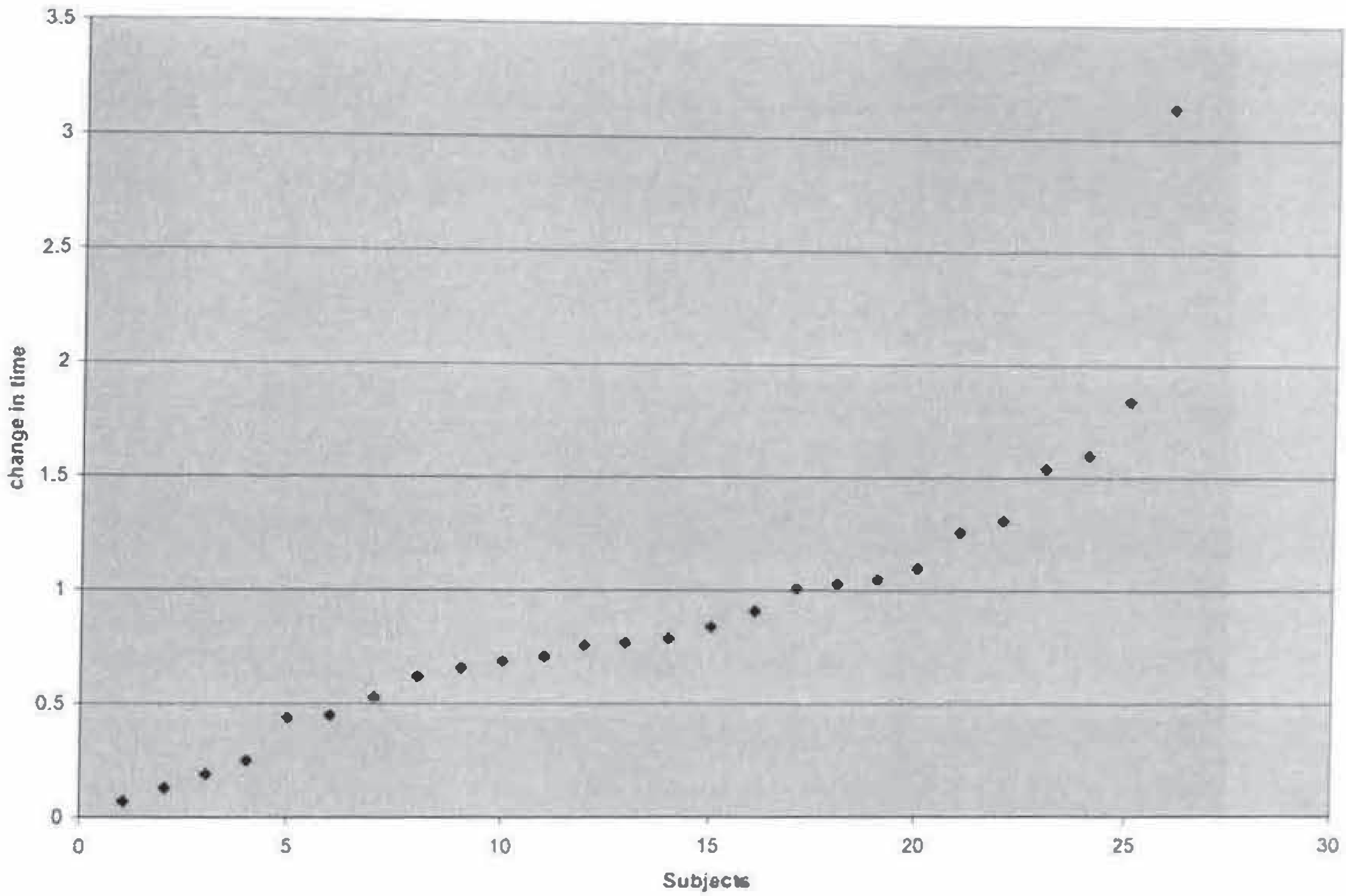


Figure 6. Change in distance from baseline to 4 weeks, 6 minute walk

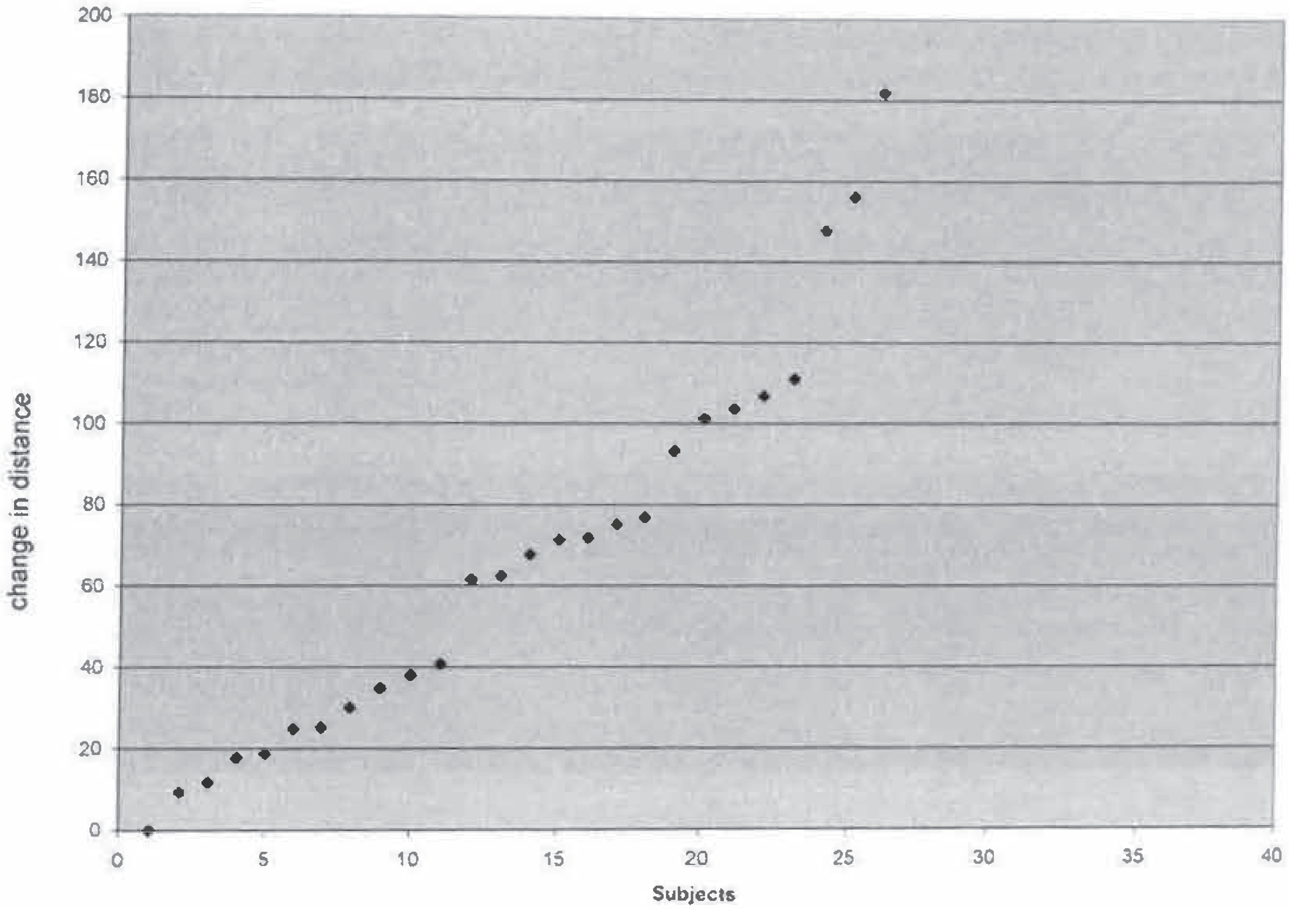


Figure 7. Change in time from 4 weeks to 8 weeks, repeated sit to stand

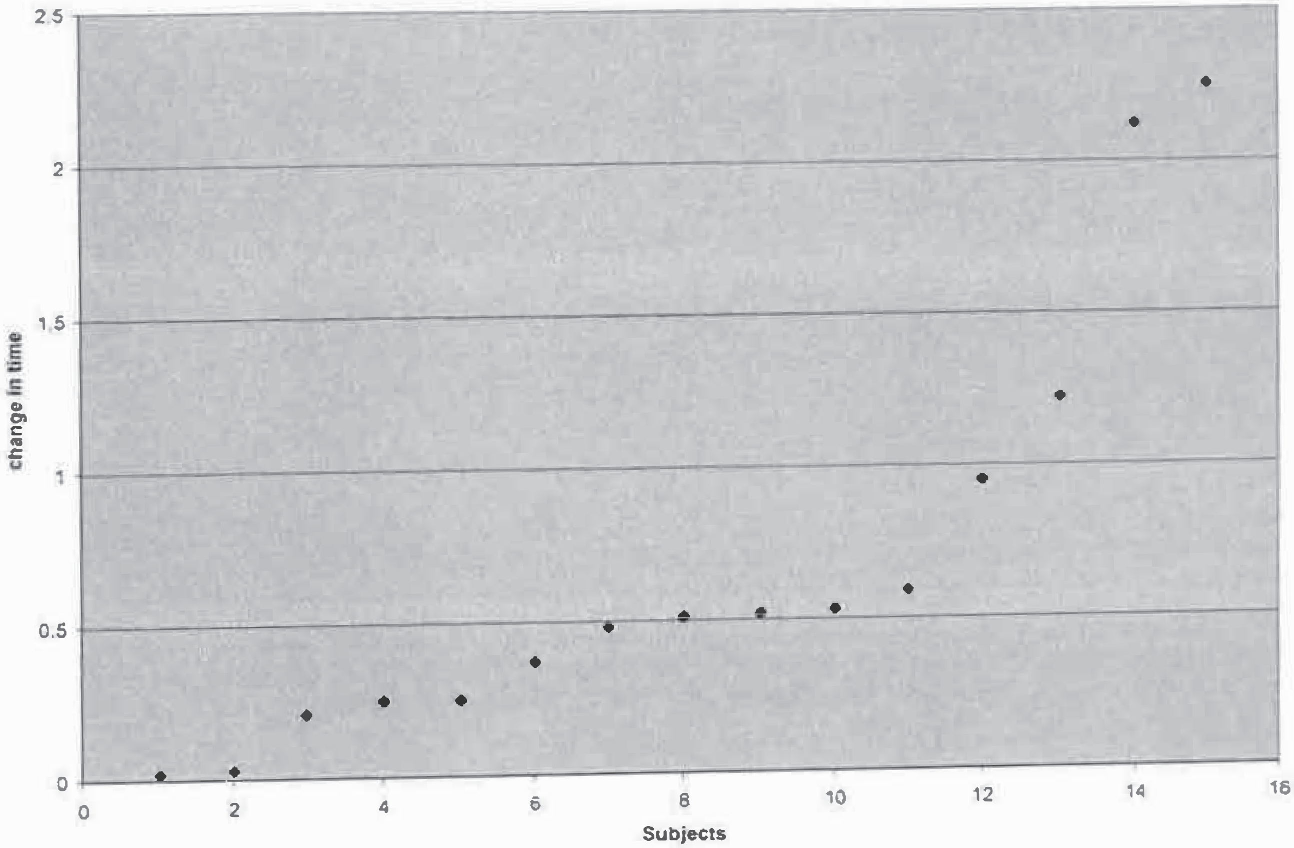


Figure 8. Change in time from 4 weeks to 8 weeks, 50 foot walk

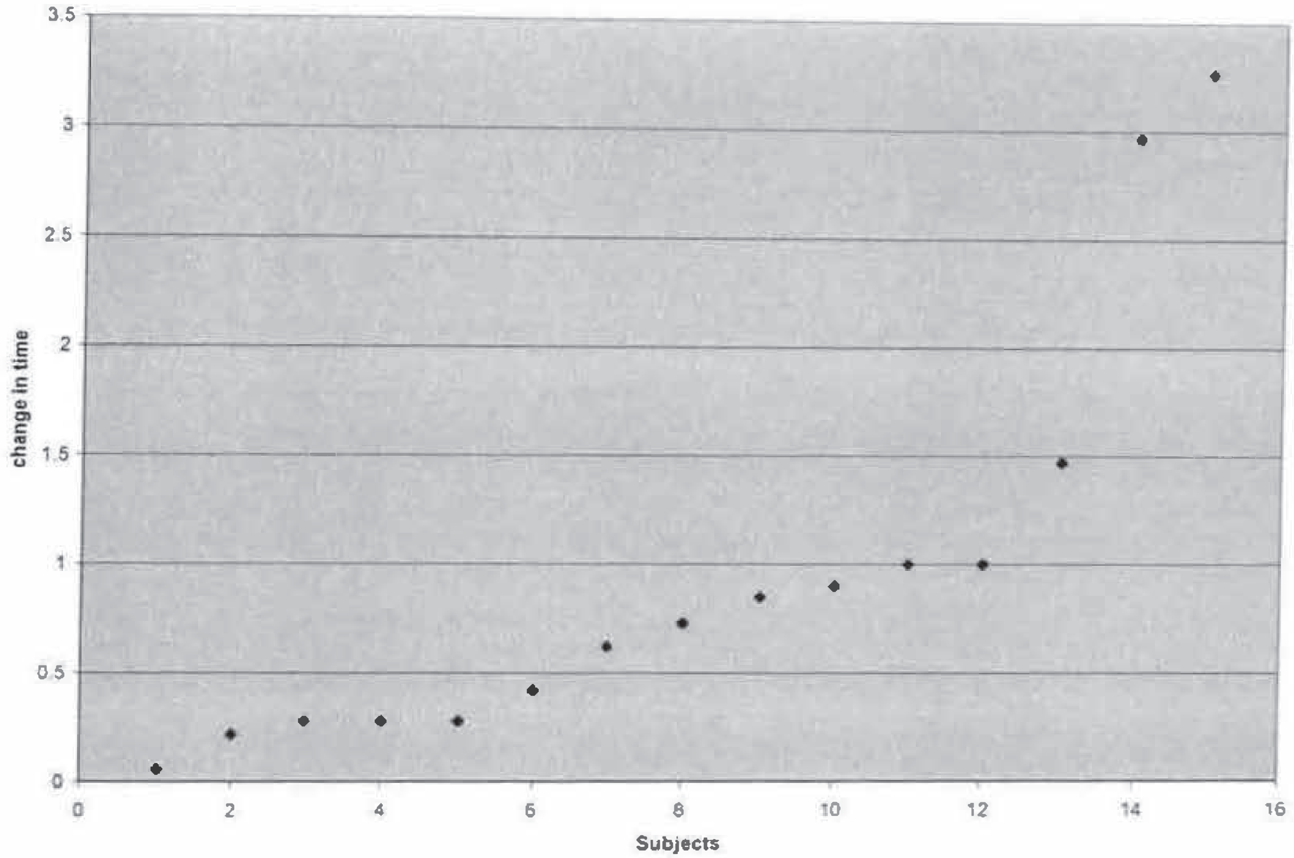
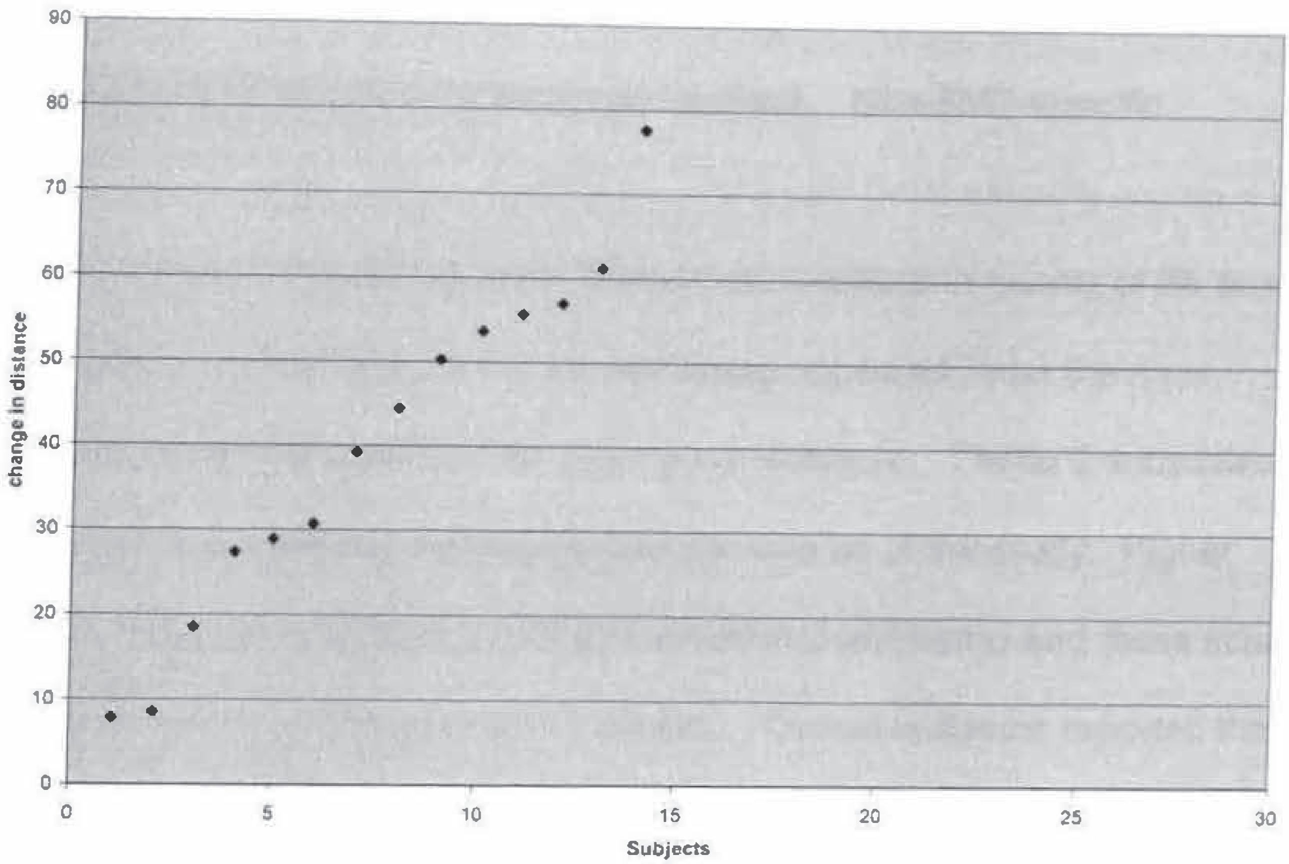


Figure 9. Change in distance from 4 weeks to 8 weeks, 6 minute walk



Descriptive statistics for the BFI, MDASI-BMT, FACT-BMT and global perception of change are presented in Table 6. The patients in our cohort reported moderate levels of fatigue (worst level of fatigue > 3) throughout the study. However, declines in fatigue severity were noted at the 4- and 8-week follow-ups compared with the baseline evaluation. As with the physical performance measures, greater gains were noted from baseline to 4 weeks than from the fourth to the eighth weeks. Total severity and interference scores followed the same pattern, with total interference scores decreasing by almost 50% after four weeks. Subjects reported severe levels of BMT-specific symptoms; these symptoms remained severe throughout the duration of the study, with the subjects reporting a higher severity at the eighth week compared to the previous assessment periods. Non-BMT-specific symptoms, however, were reported as being mild (total severity scores < 2).

The combined exercise group showed an increase in quality of life scores over time. Physical and functional well being appeared to be the most affected aspects of quality of life among our subjects. These 2 subscales demonstrated small improvements over the course of the study. Higher scores were observed with social and emotional well-being and those scores stayed relatively unchanged over 8 weeks. Overall, subjects reported that they deemed that their condition had improved moderately, and that this change was very important to them.

Table 6. Fatigue severity, symptom severity, quality of life and global perception of change scores for combined exercise group at baseline, 4, and 8 weeks (mean ± SD).

	Baseline	4 weeks	8 weeks
n	20	13	10
BFI			
Worst level of fatigue	5.33 ± 2.40	4.23 ± 2.49	3.79 ± 2.37
Total severity score	4.28 ± 1.93	3.24 ± 1.90	2.86 ± 1.60
Total interference score	4.45 ± 6.03	2.09 ± 1.70	2.13 ± 1.86
MDASI-BMT			
BMT subset	6.17 ± 4.68	6.83 ± 6.13	8.15 ± 6.43
Total severity score	1.73 ± 1.13	1.65 ± 1.37	1.55 ± 1.11
Total interference score	2.80 ± 3.43	2.01 ±1.99	1.96 ± 2.07
FACT-BMT			
Physical well being (0-28)	19.69 ± 5.04	21.74 ± 4.34	21.37 ± 5.75
Social well being (0-28)	23.78 ± 3.01	23.91 ± 3.42	23.74 ± 3.12
Emotional well being (0-24)	20.19 ± 3.56	20.52 ± 3.49	20.74 ± 3.35
Functional well being (0-28)	15.78 ± 4.57	16.48 ± 5.00	17.00 ± 6.05
BMT subscale (0-36)	27.92 ± 5.37	28.65 ± 5.43	28.95 ± 5.34
Total FACT-BMT score (0-144)	107.64 ± 13.80	111.30 ± 15.35	111.79 ± 18.00
Global perception change			
Magnitude of change (-7 -7)		4.00 ± 2.81	5.79 ± 1.97
Importance of change (-7 -7)		4.84 ± 2.45	6.37 ± 1.01

The correlations between the physical performance tests and self-report measures (BFI, MDASI-BMT, FACT-BMT) are presented in Table 7. Among the physical performance tests, functional reach was significantly associated with fatigue severity, and the 6-minute walk was significantly correlated with symptom interference with general activities. Relatively strong correlations were apparent between total symptom severity and total fatigue severity. Quality of life, in particular physical and functional well being, was associated with symptom severity (both BMT-specific and total severity) and, to a lesser extent, fatigue severity. Stepwise regression using overall quality of life as the dependent variable with age as a covariate and the physical performance tasks and fatigue and symptom severity as independent variables revealed that that the BMT-specific symptom severity was the only significant predictor of overall quality of life, accounting for 47.2% of the total variance ($R2 = .472$, $p > .0001$). Physical well-being, on the other hand, was significantly predicted by fatigue severity ($R2 = .150$, $p = .035$). The 6 minute walk and BMT-specific symptom severity were significant predictors of fatigue severity, taking age into consideration. These 2 variables accounted for 20.8% and 19.7% of the variance respectively ($R2$ change = .208, $p = .002$, and $R2$ change = .197, $p = .014$, respectively).

Table 7. Pearson's product moment correlations between physical performance tests and self-report measures for combined exercise group

	Physical performance test				**BFI**			**MDASI-BMT**		
	Sit to stand	50 ft. walk	6 min. walk	Func. reach	Worst fatigue	Total severity	Total interfer-ence	BMT subset	Total severity	Total interfer-ence
BFI										
Worst level of fatigue	.093	-.167	.284	**-.426***						
Total severity	.102	-.108	.127	**-.398***						
Total interference	.268	-.001	-.119	-.110						
MDASI-BMT										
BMT subset	.105	-.110	-.115	-.141	**.419***	**.447***	.214			
Total severity	.108	-.178	-.069	-.302	**-.498***	**.545***	.196			
Total interference	.201	-.339	**-.359***	.054	-.068	.198	.351			
FACT-BMT										
Physical well being	-.183	.213	-.013	.179	**-.418***	**-.490***	-.102	**-.583***	**-.770***	-.210
Social well being	.297	.029	.046	-.209	-.081	-.153	.038	.101	.134	.022
Emotional well being	**-.416***	-.153	.070	.157	-.117	-.156	.037	-.246	-.317	-.146
Functional well being	.122	.105	.086	-.137	-.105	-.261	-.090	**-.545***	**-.506***	**-.592***
BMT subscale	.282	.167	-.091	-.111	-.279	**-.386***	-.095	-.304	-.302	-.262
Total FACT-BMT	.004	.127	.039	-.031	-.350	**-.485***	-.097	**-.584***	**-.600***	**-.392***

* significant at .05 level

Discussion

This study was intended to provide interim, exploratory information using multi-dimensional outcomes on the effects of short-term, out-patient, clinician-directed and self-directed exercise in patients after recent allogeneic BMT/PBSCT. Our results found that four weeks of a low-to-moderate intensity exercise program improved walking speed, endurance and strength for both clinician-directed and self-directed exercise groups. Moreover, these gains were maintained or increased after the exercise intervention had ended. Generally, more substantial improvements were observed after the initial 4 weeks (baseline to 4 weeks) than after the second 4-week period (4 weeks to 8 weeks). These improvements were also generally larger in the clinician-directed group compared with the self-directed group. Functional reach remained relatively unchanged for both groups, suggesting that balance was not a problem for this cohort. It is unfortunate that tests of significance could not be conducted on our data as data collection was still ongoing for the primary study. However, even within these constraints, the preliminary results are very encouraging.

In keeping with the growing importance physical therapists are placing on patients actively participating in their care and the often complicated nature of care following allogeneic BMT/PBSCT, this study evaluated the effects of two types of exercise regimens – clinician-directed and self-directed exercise. The exercise sessions were performed over a four-week period because the study collaborators wanted to determine whether measurable changes could be observed within a time frame that was shorter than those previously reported and while the patients were no longer confined in the hospital. Past studies on post-BMT/PBSCT have reported exercise interventions lasting from 6 weeks to 12 weeks,[20, 21, 25, 84, 26] or just lasting through the patients' hospital stay.[23, 24] Moreover, four weeks was a common time frame in which many patients' third party payers required a follow-up assessment of the patients' condition. Very marginal power was found for differences between groups. A slow recruitment rate, as well as a relatively high subject attrition rate, could have been contributing factors to the marginal power.

Recruiting patients for this study proved to be a challenge. It is possible that the lower frequency of allogeneic transplant procedures performed compared to autologous transplants, as well as the many medical complications post-allogeneic transplant, may have posed as hurdles in subject recruitment. Many of the subjects initially approached chose not to participate in the study because they reported feeling overwhelmed or were too occupied with other medical procedures. Subject attrition was also relatively high; previous studies on exercise programs in cancer patients have reported completion rates of 52 – 82%.[75, 22, 10, 115, 15] Roughly 33% of our patients did not complete the 4-week evaluation, and another 30% failed to complete the 8-week evaluation. Many of these patients dropped out because of treatment-related complications requiring hospitalization, underscoring the adverse transplant -related problems [22, 35, 44, 142] or because of the aggressive treatment protocols. For this sample, subjects most likely to complete the 4-week exercise intervention were relatively younger, Caucasian, and reported that they always/often exercised before their BMT/PBSCT. It was certainly a possibility that it was the stronger subjects that were able to complete the study, and the weaker subjects self-selectively did not complete the study. However, there were no differences found in the baseline physical performance tests and self-reports between the subjects that completed the study and those that did not, thus negating that premise.

Self-efficacy, or how much confidence a person has to participate in physical activity under different constraints, has been found to be positively associated with participation in exercise.[97] A wide range of confidence was expressed by the subjects regarding their abilities to participate in exercise in the face of commonly identified barriers to exercise. Subjects were most confident about their abilities to follow instructions and to exercise at least three times a week. Intention to exercise, along with attitude and perceived behavioral control, has been found to be a determinant to exercising during cancer treatment.[98] However, a little less than half of our sample (17/40) also reported that they seldom or never exercised prior to their BMT/PBSCT. Previous studies have noted the challenges of promoting exercise adherence in patients during cancer treatment,[114, 117, 93] although similar adherence rates have been reported in breast cancer patients who were on either a self-directed or supervised walking program.[117] Anecdotally, several subjects, particularly in the self-directed exercise group, reported during follow-up conversations that while they had often intended to exercise, it was often difficult for them because of time or energy constraints, and that they were inconsistent about making up for missed days. Many of them, in fact, would do their walking exercises around the treatment area while waiting for their infusions to finish, or would complete the walking in smaller segments rather than walking continuously for a longer period of time. Many subjects in the clinician-directed group, on the other hand, were very positive about their exercise program and expressed appreciation about its flexible nature and clinician supervision. It was also observed, as evidenced by clinic logs and phone conversations with the subjects, that a majority of the patients in both groups exercised more consistently during the beginning of the study compared with the latter part.

The subjects in our cohort had better physical performance tests results compared to the mixed cancer cohort in Simmonds' study,[135] even before the start of the exercise period. These higher levels of physical performance may be attributed to the lower toxicities observed in post-allogeneic transplant patients early after transplant.[143] Our subjects were, on average, about a month post-transplant, well within the time frame before complications such as GVHD may appear. What is remarkable, though, is that physical performance, on average, improved or was maintained over time instead of declining. Moreover, these improvements were noted even as the patients were complaining of moderate levels of fatigue throughout the 8-week evaluation period, as well as many BMT-specific symptoms such as feeling physically sick, having diarrhea or mouth sores. In fact, the scores for the BMT-specific symptom severity were much higher at the 8-week evaluation than at baseline. Within the time period measured in this study, preliminary data suggest that both clinician-directed and self-directed exercise programs are beneficial for this group of patients.

Perceived fatigue, which has been cited as a major problem for many cancer patients, [144, 22, 145] was also a problem for the patients in our sample. A majority of our sample reported some fatigue; the mean values for "worst level of fatigue" reflected moderate levels of fatigue.[139] These levels steadily decreased throughout our 8-week evaluation period. Indeed, reduction in fatigue levels has been a consistent finding in studies examining exercise in many oncological populations.[7, 22, 9, 10, 146] In contrast, BMT-specific symptom severity actually increased over the 8-week evaluation period, which is not surprising as many patients started complaining about post-transplant complications such as being physically sick or beginning GVHD manifestations. In spite of these treatment-related side effects, the patients' physical performance did not appear to be too adversely compromised. According to global change scores, a vast majority of the patients (13/18) perceived their condition had improved "quite a bit" (or more) by the end of 8 weeks, and that this change in their condition was very important to them. While these results may be due to improved physical function, they may also be partly due to the patients' improved capacities to manage their fatigue and/or their other symptoms. Also, several of the BMT-specific symptoms addressed in the MDASI-BMT such as diarrhea, mouth sores, bleeding, or concentration may not directly affect the patient's strength, walking speed, or endurance. Mean values at 8 weeks for both BFI and MDASI-BMT total and interference scores were lower compared to the severity scores, particularly with the MDASI-BMT. The discrepancy in scores may reflect the fact that the total scores are mean values that were influenced by the relatively large number of subjects who reported a "0" (e.g. fatigue does not interfere, or symptoms do not interfere) on some of the questionnaire items such as "fatigue/ symptoms interfere with mood," or "fatigue/ symptoms interfere with relations with other people."

Poor quality of life has been reported by many patients post-BMT.[147] In our sample, as seen in Table 6, physical and functional well-being were the most affected aspects of quality of life. These construct values were much lower compared to normative scores reported by a healthy population.[148] Subjects also scored low on the BMT subscale. Both groups demonstrated improvements in physical and functional well being and in the BMT subscale at both the 4-week and 8-week evaluations. Similar benefits have been reported with exercise for patients with mixed cancer diagnoses.[14, 15, 149] Higher scores were evident on the patients' emotional and social well being. Moreover, relatively little variation was found over time. These results could be attributed to the emotional and family support experienced by many of the subjects during their post-transplant treatment. Diez-Campelo and colleagues, tracking the quality of life in patients from 7 days to 1 year post-allogeneic and autologous transplants, reported similar patterns, where functional well being was relatively affected while social/ family well being were not.[143] Poorer overall quality of life was associated with both greater fatigue severity and BMT-specific symptom severity. Similar relationships were evident for both physical and functional well being. These relationships suggest the possible influence of fatigue and/or BMT-related symptomatology on quality of life, particularly its physical and functional aspects.

The findings presented here must be viewed within the context of the study's limitations. Low subject numbers, with a relatively high attrition rate reflected recruitment and retention challenges when dealing with this particular patient group. The small sample size, particularly at the 8-week follow-up, coupled with the inability to conduct statistical tests of significance on the sample at this point due to ongoing data collection for the primary study, prevented a more comprehensive analysis of the results. The generalizability of these results is also then a consideration. It is unknown whether changes in the subjects' exercise and activity patterns occurred during the course of this study because the subjects could have discussed their exercise regimens with one another as most of them received their medical treatment or follow-ups in the same area of the hospital. Additionally, although improvements over time in physical performance, fatigue severity and quality of life are most likely due to participation in exercise, it is not entirely possible to rule out that some of the changes observed could be due to normal recuperative processes.

Preliminary results from this data set suggest that improvements in physical function and quality of life continue in the short term after the end of exercise intervention. It would be beneficial to determine whether these changes continue in the longer term (i.e. months or years afterward), especially with the potential development of chronic GVHD. Further research should attempt to adjust the dose of exercise that would benefit the post-allogeneic transplant patient most, as well as timing the start of the exercises to ameliorate the complex treatment-related side effects common in this patient population. It would also be valuable to establish whether participation in clinician or self-directed exercise can effect long-term changes in activity patterns. Collaborations with researchers experienced with exercise adherence would be useful to address strategies to ensure or improve adherence, particularly as it is such a complex issue with oncological patients.

Conclusion

Initial results suggest that patients who underwent allogeneic BMT/PBSCT can safely engage in exercise without adverse side effects. Within the short time period measured in this study, it appears that both clinician-directed and self-directed exercise regimens are beneficial for this group of patients and may result in improvements in physical performance and quality of life, and a reduction in fatigue severity. Significant moderate relationships noted between self-reported measures point to the possible influence of fatigue and/or BMT-related symptomatology on quality of life, particularly its physical and functional aspects.

CHAPTER IV

ACTIVITY AND SLEEP CHARACTERISTICS IN RECENT ALLOGENEIC BONE MARROW TRANSPLANT PATIENTS PARTICIPATING IN EXERCISE

Abstract

The purposes of this study were to describe and compare activity and sleep patterns in recent post-allogeneic BMT/PBSCT patients participating in a supervised or self-directed exercise program, and to to determine the feasibility of using actigraphy to document activity and sleep patterns in this patient population. Twenty (20) patients (12 males and 9 females, ages 22 – 71 years) participated. They were a subgroup from a larger series of studies examining outpatient rehabilitation interventions on the quality of life in patients following recent allogeneic bone marrow transplant/ peripheral blood stem cell transplant (BMT/PBSCT), and were within 6 months of an allogeneic BMT/PBSCT. Subjects were randomly assigned to a self-directed non-supervised or a clinician-directed supervised exercise group. The self-directed group received instruction on a home exercise program and walking regimen. The supervised group performed mixed aerobic-resistive exercises for 45-60 min., thrice a week for 4 weeks. Subjects were evaluated at baseline, 4 and 8 weeks with the Brief Fatigue Inventory (BFI) and the M.D. Anderson Symptom Inventory – Bone Marrow Transplant (MDASI-BMT). Objective sleep and wake activity data were obtained through continuous noninvasive monitoring using an actigraph on the

non-dominant wrist. Actigraphs were safe and acceptable as an objective measure of sleep and activity. Fatigue and altered activity and sleep patterns were significant problems among the subjects. Polyphasic activity patterns, with longer than normal sleep durations and shorter than normal sleep episode lengths were observed. Equivalent improvements in activity levels as well as fatigue severity were noted in subjects participating in both clinician-directed and self-directed exercise groups. However, these changes were not statistically significant. Further studies are needed to clarify the magnitude of fatigue and sleep disturbances in this population as well as the role exercise may play in ameliorating these symptoms.

Introduction

Bone marrow/ peripheral stem cell transplants have been used with increasing frequency to treat many hematological cancers such as leukemias and lymphomas, thanks in part to improved techniques in histocompatibility testing and hemotopoietic stem cell collection, and better supportive care, e.g. transfusion support and pharmacological agents.[30] According to statistics from the International Registry of BMT an estimated 55,000 autologous and allogeneic bone marrow transplants are performed annually.[1] Despite the benefits associated with BMT/PBSCT, such as improved relapse-free survival,[150-152] BMT/PBSCTs have also been associated with numerous sequelae such as fatigue, loss of physical performance and sleep disturbances that may affect patients' function up to a year or more post-transplantation.[51, 153, 57] Transplant-related morbidities are particularly marked among patients undergoing allogeneic BMT's,[52, 2-4] who run the risk of contracting graft-versus-host-disease (GVHD), a potentially life-threatening condition where healthy donor bone marrow or stem cells recognize the patient's tissues as foreign and attack them.[33] It has been reported that allogeneic transplant patients have up to a 50% risk of contracting acute GVHD if they receive donor cells from an HLA-identical sibling donor, and up to an 80% risk if the donor cells are from a matched, unrelated donor.[43, 44]

Exercise interventions among autologous bone marrow/ peripheral stem cell transplant patients have been shown to improve physical performance, fatigue severity, duration of pancytopenias and length of hospitalization, and retard loss of muscle mass.[18-21, 7, 22, 23, 25, 26] Exercise is also positively linked with aspects of quality of life such as physical and psychological well being.[23, 26] However, there is a dearth of empirical data regarding the effect of exercise interventions on allogeneic BMT/PBSCT patients, particularly in the recent BMT/PBSCT population. One of the few studies that have examined exercise in allogeneic BMT/PBSCT patients reported an increase in the muscle strength (measured through a strain-gauge dynamometer) of the large muscle groups in the shoulder, elbow, hip, knee and ankle compared to pre-BMT levels in patients who exercised compared to a control group who did not.[84] This study, however, only examined a single parameter (muscle strength) and did not consider other, more functional parameters. It is interesting that the exercise program used in the study was mainly aerobic in nature, but no outcomes for cardiovascular function were measured. Previous studies have mainly used supervised exercise programs. In light of the increasing emphasis on having patients take a more active part in their treatment, there is also a need to examine different types of exercise regimens or conditions (i.e., supervised vs. unsupervised) in order to determine regimens that work best for patients.

Altered activity and sleep patterns have been reported by many cancer patients. However, these are parameters that have not been systematically examined. Of the previous studies in the last few years, estimates of disturbed sleep among oncologic (including BMT patients) patients have ranged from 20% - 75%.[153, 154, 123, 130, 155-158] Fluctuating patterns of lowered activity in association with disturbed sleep have been noted in cancer patients receiving treatment, as well as those who had recently completed treatment.[130, 131, 157, 159, 15] Irregular sleep patterns and disturbances in rest/activity rhythms have been associated with higher fatigue levels, greater symptom distress and poorer physical and social health status,[130] as well as lower functional scores and higher symptom scores on quality of life questionnaires.[132] However, sleep and activity patterns can sometimes be difficult to ascertain because measurement of these issues often involve retrospective self-reports, which has some limitations. For example, patients may modify their reports depending on their mood or other symptoms at the time of assessment.[160] One method that has been generating interest of late as a direct, objective, non-invasive, long-term indicator of activity and sleep is the use of activity monitors or actigraphs.

Miaskowski and Lee, using wrist actigraphs to monitor the activities of outpatients undergoing radiation therapy over a 48-hour period, reported that the actigraphs were valid and objective measures of sleep efficiency in this population.[123] Activity monitors were also found to be reliable in measuring total physical activity (ICC 0.65 - 0.91) and had adequate association with other measures of functional status.[124] Actigraphs have been used as an adjunct to patient diaries in the determination of sleep and wake cycles and patterns.

Comparative estimates of total sleep and wake times, as well as relatively high rates of compliance, have been shown for both methods of measurement.[125-127] In fact, Eissa and colleagues found that wearing the wrist actigraph had a higher compliance rate than diary completion (90% vs. 71%, respectively).[127] It has been suggested that recording for 5 consecutive days provides a reliable estimate of mean 24-hour movement for a subject and is optimal to reach an 80% reliability in measuring physical activity.[128, 129]

While there are findings to suggest that there is a relationship between lower levels of activity, disturbed sleep, fatigue and decreased quality of life in cancer patients, there is no quantitative information regarding baseline activity levels in the BMT population. Moreover, whether or not BMT patients exhibit similar irregular patterns of activity, particularly if they are engaged in an exercise intervention, has not been addressed. In fact, very few studies have examined sleep-wake disturbances in the oncologic population as a primary study variable. More often, sleep-wake patterns have been a secondary finding of the study of other issues in the cancer experience. The purposes of this study were to determine the feasibility of using actigraphy to document activity and sleep patterns in this patient population, and to describe and compare activity and sleep patterns in recent post-allogeneic BMT/PBSCT patients participating in a supervised or self-directed exercise program.

Methods

Subjects

Twenty (20) patients participated in this study. The subjects were recruited from the Bone Marrow Transplant Service, through the BMT clinic, Ambulatory Treatment Center (ATC), and the Department of Rehabilitation Services of the University of Texas – M.D. Anderson Cancer Center. These subjects were a subgroup from a larger series of studies examining outpatient rehabilitation interventions on the quality of life in patients following recent allogeneic bone marrow/peripheral stem cell transplantation. Primary diagnoses were lymphoma or leukemia; subjects had undergone an allogeneic bone marrow or peripheral blood stem cell transplant within the last six months from the time of recruitment. They were receiving follow-up care in the Ambulatory Treatment Center and had been referred for Physical Therapy. Subjects were all ambulatory, although they were allowed to use an assistive device if necessary. Participants were able to perform most self-care activities independently, requiring no more than moderate assistance (no more than 50% assistance).

Patients were excluded from the study if they were less than 17 years of age, or if they had a psychiatric diagnosis, significant cardiovascular disease, hemiplegia, or paraplegia. They were also excluded if they could not speak or understand English. Subjects were told that they could ask to be removed from the study if they wished.

Measures

Activity and sleep patterns

Ambulatory physical activity levels were assessed using an actigraph accelerometer (Mini Motionlogger; Ambulatory Monitoring Inc., Ardsley, NY). Figure 1 shows the actigraph used in the study. The actigraph is a compact, lightweight (1" diameter x .035" height, 14 g.) wrist-worn unit that provides continuous, noninvasive monitoring of the patient's activity level. Figure 1 shows the Mini Motionlogger actigraph. The device has a non-volatile 32K memory with a 2-3 Hz bandwidth and 16 Hz sampling rate. Activity monitors have been found to be reliable in measuring total physical activity (ICC 0.65 - 0.91) in a cancer patient population and have adequate association with other measures of functional status.[124]

Figure 1: Mini Motionlogger actigraph

Previous reports have found comparable activity measurements between the dominant and non-dominant wrists, as well as relatively high correlations existing between wrist, trunk and ankle movements ($r = .76 - .81$).[128, 161] Activity level was measured in one-minute epochs, and activity data was collected in the Proportional Integrating Mode (PIM) mode of operation. The PIM measures movement intensity by summing the deviations from zero volts, i.e., the absolute value of the voltage, each 0.1 second during the epoch and stores the value at the end of each epoch. Each epoch (time frame recorded by the actigraph) is one minute. Figure 2 illustrates the PIM mode. Thus, greater deviations from zero volts presents as a higher bar on the actigram, which in turn implies a more vigorous or higher activity level.

Data collected by the actigraph was downloaded to a computer via the Interface unit and ACT computer software (Ambulatory Monitoring Inc., Ardsley, NY). The ActionW software (Ambulatory Monitoring Inc., Ardsley, NY) was used to score sleep and wake activities, plot linear actigrams, and calculate summary statistics. Sampling over the course of at least five continuous days of monitoring is sufficient to obtain at least 80% reliability.[129] Thus, to try to provide consistency among all the subjects, actigrams were edited to five continuous days of monitoring. Definitions of the measures used to characterize activity and sleep patterns of the subjects are described in Table 1.

Figure 2: The area in blue represents the PIM mode. The area under the curve is a measure of activity level or intensity.

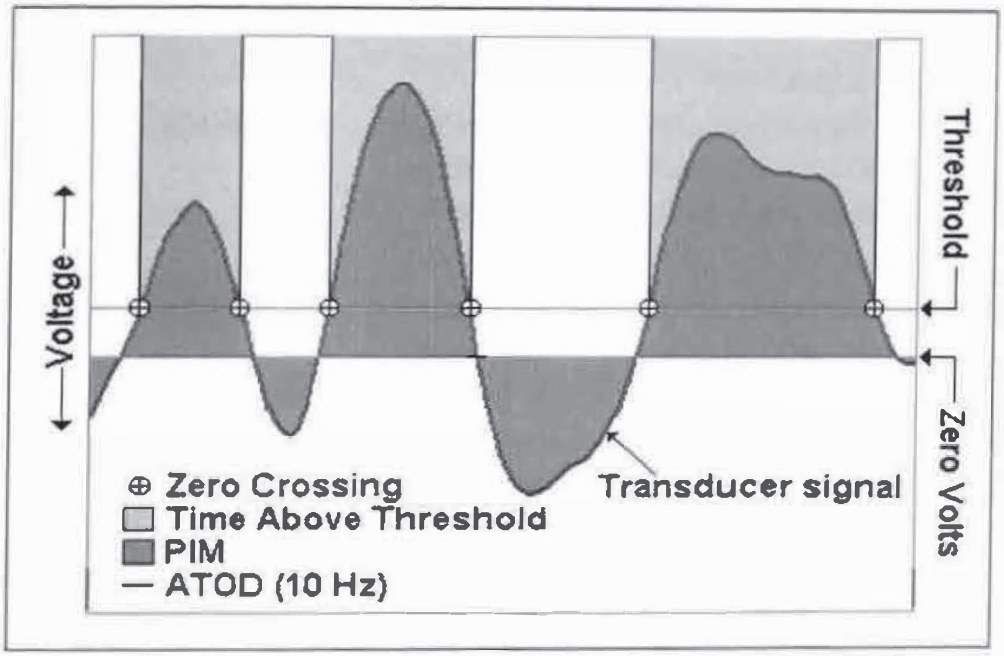


Table 1. Measures of activity and sleep obtained from the actigraph for this study

Actigraph parameter	Definition
Activity level/activity counts (activity mean)	The deviations from zero volts, i.e., the absolute value of the voltage, are summed across epochs. Each epoch (time frame recorded by the actigraph) is one minute. This is then averaged over a 5-day period to provide a value for "activity level" in a typical minute of each day.
Acceleration index	Change in activity rate during an interval. The higher the number, the higher the activity intensity
Duration of sleep (sleep minutes)	Total number of one-minute epochs scored as sleep (sleep + light sleep), averaged over a 5-day period to provide a value for "duration of sleep" in a typical night.
Mean sleep episode length	The sum of the number of contiguous one-minute epochs during each episode of sleep during the down interval, averaged across a 5-day period to provide a single value for "sleep episode length" in a typical night. The down interval is defined as the major sleep period of the day, when subjects are in bed and trying to sleep.
Percentage sleep	Sum of the number of one-minute epochs scored as sleep during the down interval, divided by the total number of epochs, multiplied by 100.

Self-reports

Brief Fatigue Inventory (BFI): a self-administered assessment of fatigue severity. The BFI characterizes the presence and impact of fatigue on function; its reliability and validity have been established in patients with cancer.[139] It consists of 9 items measured on a numeric scale from 0-10, with 0 being “no fatigue”, or “fatigue does not interfere” and 10 being “fatigue as bad as you can imagine”, or “fatigue completely interferes”. The BFI items used for this study were “worst level of fatigue in the last week” and the activity interference items, “fatigue interferes with normal activity” and “fatigue interferes with walking ability” because of interest in functional activity. Higher scores indicate higher levels of fatigue and greater interference of activity.

M.D. Anderson Symptom Inventory – BMT (MDASI-BMT): a brief measure of the severity and impact of cancer-related symptoms. The core MDASI measures 13 cancer-related symptoms and 6 items describing how much symptoms interfered with different aspects of the patient’s life in the last 24 hours. Both the symptom scales and symptom interference scales of the MDASI exhibited high internal consistency ($\alpha \geq .82$).[140] In addition, the MDASI was highly correlated with independent indicators of disease and treatment severity. The BMT module contains the core MDASI items plus 6 additional symptoms identified as problem areas by transplantation physicians and nurses. These additional symptoms include: weakness, mouth sores, diarrhea, feeling physically sick, difficulty paying attention, and bleeding. The MDASI-BMT items used for this study were the sleep-related symptom severity items, "disturbed sleep at its worst" and "feeling sleepy at its worst." This scale is currently undergoing psychometric testing.

Procedure

Subjects who met the inclusion criteria and who agreed to participate signed an informed consent form. After being evaluated by a physical therapist, they were randomly assigned by a computer to a clinician-directed supervised exercise group (n=10) or to a self-directed, self-paced unsupervised exercise group (n=10).

Subjects in the self-directed exercise group received instruction on a Home Exercise Program consistent with the current standard of care for post-BMT patients at M.D. Anderson Cancer Center. This standard of care includes a multi-disciplinary educational session where patients receive instruction from nurses, social workers and physical therapists or physical therapist assistants. The physical therapist or assistant educates the patients on home exercises consisting mainly of a walking regimen. Patients also received information on the importance of staying active through general physical activity (i.e., walking) as well as guidance on exercise safety and possible after effects of BMT/PBSCT (e.g., steroid myopathy, peripheral neuropathy, infection control).

Subjects in the clinician-directed exercise group took part in a structured exercise program. These exercises were performed in the Rehabilitation

Services gym under the supervision of a physical therapist and physical therapy assistant. This exercise program was tailored to the patients' needs and included aerobic exercises (walking on a treadmill or biking on an ergometer) and resistive exercises (free weights and machines). Each exercise session lasted approximately 45-60 minutes, thrice a week. The sessions were scheduled to coincide with the patient's scheduled visits to the Ambulatory Treatment Center for intravenous fluids or medical monitoring. This was done to encourage the patients to attend the exercise sessions, as they would not have to schedule a special trip to the facility. The entire exercise program lasted four weeks.

After baseline evaluation with the BFI, and MDASI-BMT, the subjects were shown the actigraphs and instructed on their use. The actigraphs were worn continuously on the non-dominant wrist and were initialized to begin recording as they were donned. The BFI, MDASI-BMT and actigraphy data were collected again at 4- and 8-week follow-up periods. After each actigraph data download period, the actigraphs were returned to the subjects and they were instructed to continue wearing them. There were regular weekly telephone calls to remind patients to wear their actigraphs, and to verify that the actigraphs were being worn properly.

Data Analysis

Data from this study were analyzed using SPSS version 11.5 (SPSS, Chicago, IL) for Windows software (Microsoft Corp., Redmond, WA). Descriptive statistics (means, standard deviations) were used to summarize sample characteristics as well as for the physical performance tests and self-reports. For the actigraph data, the ActionW software (Ambulatory Monitoring Inc., Ardsley, NY) was used to score sleep and wake activities, plot linear actigrams, and calculate summary statistics. Split plot 2 x 3 (group x time) ANOVAs were performed to compare the supervised clinician-directed exercise group and the self-directed exercise group over time. The variables examined were the actigraphy parameters, fatigue severity, and related MDASI-BMT symptom severity. Post-hoc pairwise comparisons were performed as needed. An alpha level of $p \leq 0.05$ was considered significant.

Results

The subjects ranged in age from 22 – 71 years (mean = 45.29, SD = 12.60). As summarized in Table 2, the majority of the sample were Caucasian and were within 3 months post-allogeneic BMT/PBSCT. There were relatively the same number of males and females. There were no significant differences between groups on all of the demographic variables ($p \geq 0.20$). About 2/3 of our subgroup, 7/11 (63.63%) from the supervised exercise group and 6/10 (60%) from the self-directed exercise group reported that they never or seldom exercised prior to their BMT/PBSCT.

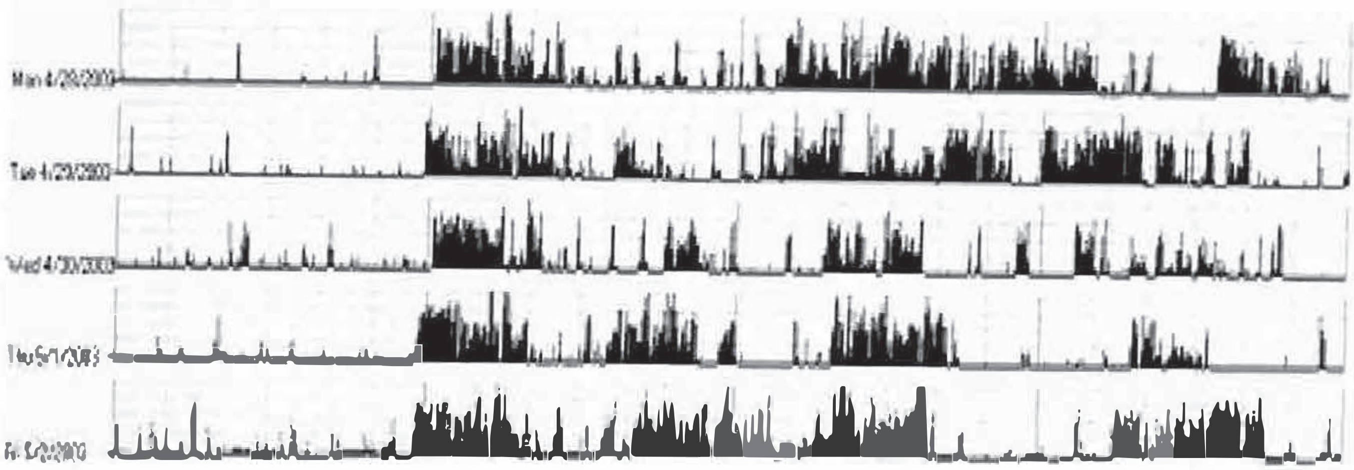
Table 2. Subject characteristics (mean ± SD)

	Clinician-directed Exercise	Self-directed Exercise
n	9	7
Age (years)	39.00 ± 11.93	44.10 ± 12.31
Gender		
Male	5	4
Female	4	3
Ethnicity		
Caucasian	7	6
Hispanic	2	1
Other		
Type of cancer		
Leukemia	4	4
Lymphoma	5	3
Time since BMT (days)	33.62 ± 13.89	29.50 ± 5.97

Actigraphy

Baseline actigraph data were available for 16 out of the 20 subjects (80%). Of these, 9 were in the clinician-directed exercise group, and 7 were in the self-directed exercise group. Actigraph data were lost due to equipment malfunction (1 subject), patient discomfort and non-compliance (2 subjects) and patient dropping out of study (1 subject). Most of the subjects reported little or no difficulty wearing the actigraph. Figure 3 shows an example of an actigraph tracing over a 5-day period. The black spikes represent the total deviation from zero volts in one minute and denote periods of wakefulness and activity; the red lines indicate periods of sleep. Daytime periods of sleep were confirmed through follow-up with the subjects.

Figure 3. Sample actigraph sleep and wake readings for 1 patient. Sleep episodes are in red.



Activity characteristics of the subjects in the clinician-directed and self-directed groups are presented in Table 3. Subjects generally adhered to conventional diurnal cycles, getting out of bed between 5 a.m. and 10 a.m. and returning to bed between 9 p.m. and 1 a.m. While mean activity counts in the PIM mode were generally unchanged over the 8-week study period in the self-directed exercise group, a small but steady increase was noted in the supervised clinician-directed exercise group. However, this change in activity counts over time was not significant (p=.34); there was also no statistically significant difference between the two groups (p=.11), nor was there a statistically significant interaction (p=.29). The acceleration index represents the change in activity rate during a 24-hour interval, with a negative value representing slowing during the interval, and a positive value representing acceleration. The acceleration index for both groups stayed about 0.20 throughout the study period ($p > 0.3$), with no group x time interaction ($p = .10$).

On average, subjects from both groups reported moderate levels of fatigue severity during the baseline evaluation. Fatigue levels decreased steadily during the course of the study; however, no statistically significant differences or interactions were noted between the two groups and over time ($p \geq 0.5$). There was a lower interference of fatigue to general activities as well as walking, particularly in the supervised group from baseline to the 4-week evaluation period. In contrast, interference of fatigue with general activities and walking stayed relatively unchanged in the self-directed group. However, there were no statistically significant differences found between groups, within the three evaluation periods, or group x time interaction for interference with general activities ($p \geq 0.4$) and interference with walking ($p \geq 0.4$).

Table 3. Change in activity characteristics (mean ± SD) of recent allogeneic BMT/PBSCT patients in supervised clinician-directed and self-directed exercise groups

	Supervised clinician-directed			Self-directed		
	Baseline	4 weeks	8 weeks	Baseline	4 weeks	8 weeks
n	8	8	8	7	7	7
Mean activity counts	5299.77 ± 836.67	5469.96 ± 1570.75	5865.86 ± 1040.25	4681.84 ± 1979.72	4018.37 ± 1503.19	4159.65 ± 1615.74
Acceleration index	.20 ± .05	.22 ± .08	.21 ±. .08	.20 ±. .08	.22 ± .08	.22 ± .08
BFI fatigue severity	5.67 ± 2.16	5.00 ± 2.91	4.50 ± 1.79	4.80 ± 3.27	4.80 ± 3.27	4.20 ± 3.11
BFI interferes with general activity	4.00 ± 2.64	2.40 ± 2.88	2.20 ± 2.80	2.70 ± 2.17	2.20 ± 1.20	2.60 ± 2.30
BFI interferes with walking	3.50 ± 1.86	3.20 ± 3.27	3.00 ± 2.24	2.50 ± 3.90	2.40 ± 1.52	2.60 ± 3.00

* indicates $p \leq .05$

On the whole, subjects slept from 6 hours to 15 hours per night. However, their sleep was quite disjointed with mean sleep episodes for subjects in both groups lasting less than 50 minutes throughout the 8-week study period. Changes in sleep characteristics are summarized in Table 4. Duration of sleep for the clinician-directed group shows a decrease from baseline to the 8-week follow-up period. In contrast, the self-directed group had a slight increase in sleep duration in the same time period. However, there was no interaction, and these changes were not statistically significant, both over time within each group and between the two groups ($p \geq 0.3$).

A number of night awakenings were also observed for all the subjects, in general increasing in frequency in the eighth week compared to the first. Night awakenings were primarily for discomfort or trips to the bathroom. Thus subjects spent an average of 85 – 91% of the night asleep. There were also sleep episodes throughout the daytime, particularly in the late afternoon.

Disturbed sleep scores in the MDASI-BMT for both groups were a little higher at 4 weeks compared to baseline and then came back down at the 8-week evaluation. These changes, however, were not significant for time ($p = .31$) or group ($p = .32$) or time x group interaction ($p = .6$). Likewise, subjects' self-reports of feeling sleepy at its worst improved over the 8-week period, but the changes were not enough to be statistically significant over time ($p = .2$), group ($p = .55$) or group x time interaction ($p = .6$)

Table 4. Change in sleep characteristics (mean ± SD) of recent allogeneic BMT/PBSCT patients in supervised clinician-directed and self-directed exercise groups

	Supervised clinician-directed			**Self-directed**		
	Baseline	4 weeks	8 weeks	Baseline	4 weeks	8 weeks
n	8	8	8	7	7	7
Duration of sleep (min.)	669.29 ± 176.95	677.15 ± 153.04	639.60 ± 122.35	655.22 ± 170.52	688.97 ± 149.66	686.24 ± 201.30
Mean length of sleep episode (min.)	41.15 ± 4.25	47.40 ± 11.56	41.76 ± 5.98	47.52 ± 10.50	45.97 ± 8.4	48.86 ± 10.02
Percentage of sleep	90.32 ± 4.57	91.19 ± 7.08	89.96 ± 4.41	84.43 ± 10.24	86.63 ± 6.77	88.69 ± 3.91
MDASI-BMT "disturbed sleep at its worst"	3.75 ± 2.31	4.57 ± 3.35	3.00 ± 2.58	2.89 ± 2.00	3.50 ± 3.39	2.83 ± 3.06
MDASI-BMT "feeling sleepy at its worst"	3.50 ± 2.20	3.29 ± 2.75	2.14 ± 1.86	2.33 ± 3.28	2.67 ± 2.94	1.83 ± 2.14

* indicates $p \leq .05$

Discussion

This study described and compared the activity and sleep characteristics in recent allogeneic BMT/PBSCT patients participating in a short-term clinician-directed or self-directed exercise program. Small but steady gains in activity level, as well as a decrease in self-reported fatigue severity and interference were noted, particularly in the patients who participated in a supervised exercise program. Moreover, these gains were maintained after the exercise intervention had ended. Unfortunately these changes had modest effect sizes and were not statistically significant over the three evaluation periods, or compared to the self-directed exercise group. The small number of subjects very likely affected the power of the study, resulting in non-significance.

Subject recruitment was challenging. The numerous medical complications following allogeneic transplantation, and the lower frequency of allogeneic transplants may have been factors that contributed to recruitment difficulties. Many of the subjects initially approached chose not to participate in the study because of "just too many things going on." However, subjects who did consent to participate were very positive about the exercise programs. Anecdotally, subjects in the supervised exercise group were appreciative of the close supervision by the clinician and the flexible scheduling. On the other hand, some of the subjects in the self-directed exercise group reported that they liked that they could do their exercise activities in self-paced segments.

Perceived fatigue, which has been recognized as a significant quality of life issue for many cancer patients [144, 22, 145] was also a problem for the patients in our sample. A majority of our sample reported some fatigue; the mean values for "worst level of fatigue" reflected moderate levels of fatigue.[139] Fatigue severity was lower at both 4 and 8 weeks for both supervised and self-directed exercise groups compared to baseline, more so in the former. Though statistically insignificant with our small sample, this decline in fatigue levels mirrors consistent results from other studies that have investigated exercise in various cancer diagnoses. [9, 10, 146] While these improvements may be due to the patients improved functional capacity, they may also point to the patients' improved abilities to manage their fatigue.

The viability of using actigraphs as a measure of activity and sleep was determined in this population. Almost all of the subjects reported no difficulty using the actigraph. The actigraph used in this study was about the size of a wristwatch. Once donned, most were able to carry on with their exercises and daily activities without hindrance.

Lowered or altered activity levels, as well as disturbed sleep have been reported in cancer patients.[154, 130, 156, 157, 159, 15] In this study, objective measures of activity and sleep showed a great amount of variability. Although subjects generally followed conventional diurnal cycles, the range of times when they got out of bed or returned to bed was about 5 hours. In addition, sleep was fairly fragmented, with frequent night awakenings, usually due to nocturia or discomfort. Other studies with cancer patients have also reported irregular sleep patterns due to pain, leg restlessness, feeling too hot, or coughing.[162, 123, 157] The activity patterns of the subjects also exhibited a polyphasic rhythm with less differentiation between day and night. These patterns suggest daytime naps and decreased daytime activities, instead of the more conventional pattern where activity takes place during the day and rest occurs only at night. There were several sleep episodes noted during the daytime, especially towards the late afternoon, which may have been due to subjects feeling more tired at the end of the day and thus trying to nap or rest during that period.

Average night time sleep duration for our sample were approximately 10 to 12 hours, with average sleep episodes lasting 42 to 48 minutes. These data show a considerably longer than normal duration of sleep, but with much shorter sleep episode lengths. In a 24-hour period, seven to nine hours of sleep, with sleep episodes lasting 90 – 110 minutes, are deemed typical.[163] The average sleep episodes observed in this study are similar to those that Young-McCaughan and colleagues reported, with average sleep episodes lasting about 48.5 minutes in a cohort with mixed cancer diagnoses.[15] Sleep percentage ranged from 85 to 91% over the 8-week study period, suggesting a disturbed sleep. In a typical night, a sleep percentage of greater than 95% would indicate a good night's sleep, while less than 85% indicates a bad night's sleep. [123]

It is interesting that even though the subjects in this study spent a good part of the day sleeping, their self-report of feeling sleepy was relatively mild (≈ 3/10). Perhaps the subjects underestimated the magnitude of this symptom. Disagreements between objective data and subjective reports have been noted in other studies.[164, 123, 15] It is also possible that there were some periods scored as sleep by the actigraph when in fact the subject was lying awake but not moving very much. There are some other limitations to actigraphs that are noteworthy. Analysis of actigraphy tracings can sometimes be open to interpretation. Tracings only depict activity frequency and intensity, and do not differentiate between similar activities of differing difficulty levels, for example, walking uphill versus walking on level ground.

This study had a small sample size, so the results may not be representative of the entire population of recent post-allogeneic transplant patients. In addition, there was a lack of a control group. Any changes over time that may have occurred might be a result of normal recuperative processes or better management of symptoms by the subjects.

Additional research is needed to more clearly describe activity and sleep patterns using both objective and subjective measures. It would also be beneficial to investigate the correlates and/or predictors of disturbed sleep which would provide useful information for the development of interventions that may be helpful in managing this problem. Further research should address the advantages and disadvantages of clinician-directed and self-directed exercise programs and whether one or the other is better suited to certain types of patients or certain time periods during treatment.

Conclusion

Findings from this study suggest that actigraphs are an acceptable objective measure of sleep and activity. Fatigue and altered activity and sleep patterns were significant problems among recent post-allogeneic BMT/PBSCT patients. Polyphasic activity patterns, with longer than normal sleep durations and shorter than normal sleep episode lengths were observed. Activity levels and fatigue severity trended towards improvement in both subjects participating in both clinician-directed and self-directed exercise groups. Though there was anecdotal evidence that these changes over time were viewed positively by the subjects, they were unfortunately not statistically significant. Further studies are needed to clarify the magnitude of fatigue and sleep disturbances in this population as well as the role exercise may play in ameliorating these symptoms.

CHAPTER V

ASSESSING THE OUTCOMES OF AN EXERCISE INTERVENTION FOLLOWING RECENT ALLOGENEIC BONE MARROW TRANSPLANTATION: A CASE SERIES

Abstract

The purpose of this case series was to examine physical performance outcomes of an 8-week outpatient exercise regimen, and to describe fatigue severity and sleep and wake activity patterns in four patients following recent allogeneic BMT. Four subjects, 2 males and 2 females, with mean age 38.75 ± 9.88 years were studied. All were less than 3 months post-allogeneic bone marrow/peripheral stem cell transplant (range 35-64 days). Two subjects participated in an 8-week supervised exercise program that included aerobic and resistive exercises. Each exercise session lasted 45 – 60 minutes, three times a week. Two subjects participated in a self-directed non-supervised exercise regimen. The following assessments were completed at baseline and after 4 and 8 weeks: physical performance measures (timed sit-to-stand, 50-ft. fast walk, 6-minute walk, and forward reach), the Brief Fatigue Inventory (BFI), a measure of fatigue severity, and the MD Anderson Symptom Inventory – Bone Marrow Transplant (MDASI-BMT), a measure of the severity and impact of cancer-related symptoms. Objective sleep and wake activity data were obtained through

continuous noninvasive monitoring using an actigraph on the non-dominant wrist. Both supervised and non-supervised exercises were safe and acceptable to the patients. Significant improvements were noted in strength, walking speed, and endurance, as well as fatigue severity. However, these gains were more pronounced after the first 4 weeks, and in the patients who had participated in supervised exercise. Although irregular sleep and wake patterns were observed, activity frequency and intensity were enhanced, suggesting better physical function and/or fatigue management. This case series illustrates the value of exercise in ameliorating physical decline following recent allogeneic BMT.

Introduction

Bone marrow and peripheral blood stem cell transplantation (BMT/PBSCT) represents the treatment of choice for many patients with hematological cancers such as leukemias and lymphomas. Despite the benefits associated with BMT, e.g., improved relapse-free survival, there are also numerous associated sequelae that may limit patients' function and activities.

Many patients who undergo bone marrow transplant will already have undergone previous regimens of chemotherapy and/or radiation therapy, and thus may have already-existing declines in function.[35] Common symptoms associated with BMT/PBSCT include fatigue, loss of physical performance and sleep disturbances, with many patients reporting limitations in their abilities to engage in physical activities up to a year, or more post-transplantation.[51, 153, 165] Bone marrow ablation results in cytopenias, with its related issues of developing anemia and/or infections.

Adverse effects on physical function and quality of life occur particularly in patients who undergo allogeneic BMTs.[52, 2-4] In addition to the many complications associated with BMT/PBSCT, recipients of allogeneic transplants are at risk for developing graft-versus-host-disease (GVHD). This potentially life-threatening condition is typically managed through the use of high-dose corticosteroids, with steroid myopathy, or the weakening and/or atrophy of proximal muscle groups, being a major side effect of it use.[166, 35]

Exercise has been an intervention that has been shown to beneficial for the rehabilitation of patients with chronic diseases.[71-74] For oncological patients, exercise has until quite recently, been utilized to address specific impairments caused by surgical interventions. This has been partly due to concerns that vigorous exercise may exacerbate the side effects from chemotherapy and/or radiation therapy, result in an increase in pain and/or fatigue severity, and that cancer patients are unable to tolerate exercise due to their weakened conditions.[167]

Relatively recent studies demonstrate that clinician-directed exercise following autologous bone marrow transplantation (BMT) have favorable effects on walking speed and distance,[19-21] fatigue,[21, 22] hemoglobin concentration,[22] and skeletal mass.[25] Moreover, the patients who exercised had a substantially shorter hospital stay and shorter duration of neutropenia and thrombopenia.[20] Self-directed exercise was also related to overall quality of life [26] as well as a number of quality of life domains including physical and psychological well-being.[23] However, there is little empirical data regarding the effect of exercise on physical performance and activity levels following allogeneic BMT, particularly after the patient has been discharged from the hospital. Moreover, with the growing importance placed on having patients take a more active role in their care, it becomes important to examine different types of exercise regimens (i.e., supervised vs. unsupervised) that may be available to patients. Mello and colleagues [84] reported that allogeneic BMT patients who participated in a supervised exercise program demonstrated greater gains in muscle strength than their counterparts who did not exercise. That study, though, had an exercise program that was initiated during hospitalization and evaluated only muscle strength, not other parameters. The purpose of this case series was to describe physical performance outcomes of a short-course, outpatient, supervised or non-supervised exercise regimen, and to describe fatigue severity and sleep and wake activity patterns in a small cohort of patients following recent allogeneic BMT.

Patient Descriptions

Patient A is a 28-year-old female who, after finding a lump on the left side of her neck, was initially diagnosed with Stage IIa nodular sclerosing Hodgkin's disease. She received six courses of ABVD (Adriamycin, Bleomycin, Vinblastin, Dacarbazine) at a community hospital, and was felt to have a complete response to the chemotherapy regimen. However, less than one month later she was found to have recurrence/persistence of disease in the left axilla. At that point, she was switched to ESHAP (Etoposide, Methylprednisolone, Cisplatin, Cytarabine) for three cycles but had no response. Subsequently, she was referred to M. D. Anderson Cancer Center where she received ICE (Ifosfamide, Carboplatin, Etoposide) chemotherapy for three cycles, achieving partial remission. This was followed by an autologous bone marrow transplant approximately 18 months after initial cancer diagnosis. Her post-transplant course was unremarkable until Day 100 post-transplant when during routine follow-up, she was found to have a localized recurrence of the disease in her left axilla. She was then put on liposomal vincristine for five cycles and Gemzar and Rituxan for two cycles. These led to only transient responses. Ultimately, she underwent a left axillary node resection as well as radiotherapy to the left axilla and neck, which rendered her disease-free. A month later, progression of the disease was noted on gallium scan and the patient was treated with HCVD (hyperfractionated cyclophosphamide, vincristine, dexamethasone) for two cycles with a good partial response. During this process, a sibling was identified as a BMT match. Approximately three years after her initial cancer diagnosis, after a fludarabine and busulfan preparative regimen, she underwent an allogeneic transplant using peripheral stem cells. Her counts hit nadir on Day 5; engraftment occurred on Day 11. On Day 13 she developed a fungal infection, which cleared up with anti-fungals and antibiotics. Otherwise, her inpatient stay was uncomplicated, her blood counts were stable, if relatively low (at discharge, hemoglobin was 8.5, WBC 6.9, platelets 109,000), and she was discharged as an inpatient after 26 days. She was placed on prophylactic Tacrolimus 1 mg. p.o BID, and continued to receive intravenous fluids and appropriate blood or platelet support as an outpatient.

Patient B is a 49-year-old male who was diagnosed with acute myelogenous leukemia after consulting with a physician because of a chronic cough. He received chemotherapy with idarubicin and ara-C in a 7 + 3 regimen (i.e. idarubicin given over 3 consecutive days along with ara-C given continuously over 7 days), and achieved complete remission. He was found to have a relapse almost 4 years later after complaining of fever. He was given another course of chemotherapy (daunorubicin and ara-C) and again achieved remission. A decision was made to undergo bone marrow transplantation; a few months later, the patient underwent an allogeneic bone marrow transplant from an HLA-matched brother donor. Engraftment occurred on Day 12. His post-transplant hospital stay did not have any significant complications, his blood counts were a little low, but stable (at discharge from the hospital, hemoglobin was 10.1, WBC 8.4, platelets 115,000). He continued to receive intravenous therapy and blood product support as needed as an outpatient. On Day 60, he complained of dryness of the mouth and eyes, which his physicians assessed to be secondary to mild GVHD. He was placed on Prograf (tacrolimus) alternating 1 and 0.05 mg p.o.

Patient C is a 45-year-old male who was diagnosed with chronic lymphocytic leukemia during a blood donation drive. During pre-donation screening, his WBC was found to be in the 200,000 range. He underwent chemotherapy with Chlorambucil for two months but had no response to treatment. He then received Fluradabine for five cycles and achieved total remission. However, about 18 months later he relapsed and again was treated with Fluradabine for six cycles. He relapsed two more times over the next 4 years, each time receiving Fluradabine for 6 cycles and getting a partial response. When he relapsed a fourth time, he was deemed increasingly resistant to Fluradabine and received a combination of Rituxan, Fluradabine and Cytoxan. At this time, his siblings were typed for a possible HLA match for bone marrow transplant but were found to be non-compatible. He continued to receive chemotherapy, switching to Rituxan and high dose methylprednisolone and achieving a partial response. About ten years from his initial cancer diagnosis, after a preparative regimen of Rituxan, Fluradabine and Cytoxan, he underwent an allogeneic bone marrow transplant from an unrelated donor. His counts nadired on Day 4; he engrafted on Day 10. He developed a productive cough on Day 8, which was treated successfully with antibiotics. His hospital stay was otherwise smooth, his blood counts were low but stable, and he was discharged as an inpatient on Day 13 (at discharge, hemoglobin was 9.1, WBC 3.0, platelets

39,000). He continued to receive intravenous therapy and blood product support as needed as an outpatient. His post-transplant course has been complicated by a persistent pruritic rash on his face, neck, and back (about 27% of body surface area) consistent with acute GVHD, as well as a candidal infection. He was placed on Tacrolimus o.p. prednisone and topical creams for the former condition and cefepime and voriconazole for the latter.

Patient D is a 33-year-old female who went to her physician secondary to fatigue and malaise. Her work-ups showed a mediastinal mass and pleural effusion, and she was diagnosed as having acute lymphocytic leukemia. She underwent eight cycles of CHOP (Cytoxan, Hydroxidoxyrubicin, Oncovin, Prednisone) and achieved complete remission. She was placed on a maintenance chemotherapy regimen of methotrexate for 2 years after initial diagnosis. Unfortunately, about three months after discontinuing chemotherapy, her leukemia recurred. She was treated with HyperCVAD (hyperfractionated Cyclophosphamide, Vincristine, Adriamycin, Dexamethasone) with Rituxan for three cycles and total body irradiation with a dosage of 200 cGy over 4 days. During this time, she complained of fatigue and weakness which her physicians attributed to past regimens of chemotherapy. She also had blurring of vision in her left eye secondary to Cytomagalovirus (CMV) retinitis, and which was treated with intravenous Foscarnet and Ganciclovir. After the completion of the HCVD and irradiation therapy, she underwent an allogeneic transplant using peripheral blood stem cells from an HLA-matched brother donor. Her post-transplant course was complicated by mucositis, which was managed successfully with Dilaudid pump. She engrafted on Day 12 and was discharged as an inpatient after 17 days. She continued to receive intravenous therapy and blood product support as needed as an outpatient. Her post-transplant course has been complicated by her continuing CMV retinitis and mild GVHD of the skin, manifesting as rashes on her upper extremities as well as complaints of numbness in her feet.

Table 1 outlines demographic characteristics of our subjects.

Table 1. Subject demographics.

	Subject A	Subject B	Subject C	Subject D
Age	28	39	45	33
Gender	Female	Male	Male	Female
Diagnosis	Hodgkin's disease	Acute myelogenous leukemia	Chronic lymphocytic leukemia	Acute lymphocytic leukemia
Type of allogeneic transplant	Bone marrow	Bone marrow	Bone marrow	Peripheral stem cells
Time since BMT	35 days	40 days	64 days	47 days

Examination

The patients were recruited to participate in a larger study on outpatient exercise regimens for recent allogeneic BMT recipients conducted at the Rehabilitation Services Department of M. D. Anderson Cancer Center (Houston, TX). They were evaluated by a physical therapist within 6 months of their allogeneic transplants. The patients' main complaints included fatigue, weakness and difficulty sleeping. One patient reported numbness in her feet (Patient D). Prior to their cancer diagnoses and BMT/PBSCTs, the patients reported that they were fairly sedentary and seldom or never exercised. Active ranges of motion of both the upper and lower extremities were within normal limits. Manual muscle testing was a 3/5 (fair) or 4/5 (good) in major muscles of both upper and lower extremities. The patients exhibited good static and dynamic balance in both sitting and standing, except for Patients B and D whos' dynamic balance in standing was impaired (i.e., had decreased times maintaining balance during uniped stance and with perturbations). They were all independent going to and from a supine position to a sitting position, and to and from a sitting to a standing position. All were able to negotiate a flight of stairs but did so with effort. Table 2 outlines the hemoglobin WBC and platelet levels of the patients on the day of initial evaluation.

Table 2. Hemoglobin, WBC, and platelet values for patients during PT initial evaluation. Normal ranges are in bold under column headings[168]

	Hemoglobin (g/dL) Normal range: M: 13-18, F: 12-16	WBC (thousand/μL) Normal range: 4.5 – 11.0	Platelets (/μL) Normal range: 150000-400000
Patient A	10.0	2.3	61000
Patient B	10.1	4.5	147000
Patient C	8.3	2.5	128000
Patient D	10.1	5.4	150000

Testing

Before beginning the intervention, the patients completed pre-intervention testing, which consisted of:

- physical performance measures (timed sit-to-stand, 50-ft. fast walk, 6-minute walk, and forward reach)
- the M.D. Anderson Symptom Inventory-BMT
- the Brief Fatigue Inventory

Re-assessments using the same measures were performed at the end of four weeks and at the end of eight weeks.

Noninvasive, objective sleep and wake activity data were obtained using an actigraph. Each patient was instructed on its use, and the actigraph was worn on the non-dominant wrist throughout the intervention period. Data from the actigraph was downloaded at regular bi-weekly intervals and scored according to the manufacturer-provided software.

Test Descriptions

Physical performance battery: a set of tasks where the time taken to complete the task or the distance reached is measured. These series of tasks challenge physical function, specifically speed, endurance, and balance. Simmonds[135] established the reliability, validity and clinical usefulness of this battery in patients with cancer. There was excellent test-retest reliability ($r \geq 0.8$); all tasks had face validity, and they proved acceptable to the patients. In addition, the battery was found to be moderately responsive to change and a better predictor of disability than either impairment or psychosocial measures alone. Those tests that are part of the M.D. Anderson Cancer Center – Department of Rehabilitation Services standard patient evaluation were used. The tasks are as follows:

- *50-foot walk at patient's fastest speed.* Subjects were timed as they walk a distance of 50 feet. They were told to walk as fast and as safely as they can.
- *6-minute walk.* Subjects walked as far, as fast and as safely as they can for six minutes. The distance walked was then measured and recorded.
- *Forward reach.* Subjects stood next to a wall on which a meter stick was mounted horizontally at shoulder height. The subjects stood next to the meter stick with their shoulder forward flexed to 90°, elbow extended, wrist at neutral and fingers extended. Keeping their heels on the floor, patients reached forward along the meter stick as far as they could. The distance reached was measured and recorded in centimeters.
- *Timed repeated si- to-stand.* Subjects sat on a flat surface, 18 inches in height. They were asked to rise to a standing position, without using their arms to push off, and return to a sitting position, as quickly and as safely as possible, twice.

Brief Fatigue Inventory (BFI): a self-administered assessment that characterizes the presence and impact of fatigue on function; its reliability and validity have been established in patients with cancer.[139] It consists of 9 items measured on a numeric scale from 0-10, with 0 being “no fatigue” or “fatigue does not interfere” and 10 being “fatigue as bad as you can imagine” or “fatigue completely interferes.” Higher scores indicate higher levels of fatigue and greater interference of activity. The BFI item used in this series of case studies, aside from mean total BFI score, was “worst fatigue”, which measures of fatigue severity.[139]

M.D. Anderson Symptom Inventory – BMT (MDASI-BMT): a brief measure of the severity and impact of cancer-related symptoms. The core MDASI measures 13 cancer-related symptoms and 6 items describing how much symptoms interfered with different aspects of the patient’s life in the previous 24 hours. Both the symptom scales and symptom interference scales of the MDASI exhibited high internal consistency ($\alpha \geq .82$).[140] In addition, the MDASI was highly correlated with independent indicators of disease and treatment severity. The BMT module contains the core MDASI items plus 6 additional symptoms identified as problem areas by transplantation physicians and nurses. These additional symptoms include weakness, mouth sores, diarrhea, feeling physically sick, difficulty paying attention, and bleeding. This subscale is currently undergoing psychometric testing. For this case series, we used the symptom severity score (mean of the symptom items) and mean total score.

Actigraphy: the Mini Motionlogger actigraph (Ambulatory Monitoring Inc., Ardsley, NY) is a compact, lightweight (1" diameter x .035" height, 14 g.) wrist or belt-worn unit that provides continuous monitoring of the patient's activity level. Figure 1 shows the Mini Motionlogger actigraph. The device has a non-volatile 32K memory with a 2-3 Hz bandwidth and 16 Hz sampling rate. Activity monitors have been found to be reliable in measuring total physical activity (ICC 0.65 - 0.91) in a cancer patient population and have adequate association with other measures of functional status.[129]

Figure 1: Mini Motionlogger actigraph

The actigraph was worn on the non-dominant wrist throughout the intervention period, except when bathing or swimming. Activity level was measured in one minute epochs, and activity data was collected in the Proportional Integrating Mode (PIM) mode of operation. The PIM mode totals the deviations from zero volts every .1 second during the epoch and stores the value at the end of each epoch.

Data collected by the actigraph was downloaded to a computer via an Interface unit at bi-weekly intervals. Software provided by the manufacturer allows scoring and analysis of rest and activity periods. Periods of wakefulness were further verified with the patients through interview. Five days of continuous monitoring were randomly sampled over the first two week period, and two weeks thereafter until the intervention period was over. Five days of continuous monitoring has been shown to be sufficient to obtain at least 80% reliability.[129]

Intervention

The patients were part of a larger study on outpatient exercise regimens for recent allogeneic BMT recipients. As part of this larger study, Patients A and B were randomly assigned to participate in a four-week supervised structured exercise regimen and Patients C and D were randomly assigned to a non-supervised exercise group.

Patients A and B attended thrice weekly exercise sessions, with each session building from approximately 30 minutes to approximately 60 minutes. The sessions were scheduled to coincide with the patients' scheduled visits to the Ambulatory Treatment Center for intravenous fluids or medical monitoring. This was adopted to encourage the patients to attend the exercise sessions, as they would not have to schedule special trips to the facility. Patients who undergo bone marrow transplants at M. D. Anderson are followed in the Ambulatory Treatment Center up to 5 days a week for the first hundred days post-transplant. Typically, the patient would check into the Ambulatory Treatment Center, get hooked up to intravenous fluids, then come to the Rehabilitation Services Department for exercise sessions. Throughout the four-week regimen, performance of the exercises was supervised by a physical therapist or physical therapist assistant with experience working with post-BMT patients.

The exercises prescribed consisted of both aerobic and resistance exercises. They were of a low to moderate intensity (50-70% of maximal heart rate, or 11-13 on Borg Scale for Rating of Perceived Exertion),[169] with progressions according to the patient's tolerance. The exercises were comprised of walking on a treadmill, cycling on a bicycle ergometer, and hip, knee, shoulder, and elbow exercises using Cybex Modular weight machines

(Cybex International, Medway, MA), and/or a Total Gym (Engineering Fitness International Inc., San Diego, CA). Periodic rest intervals and water breaks were provided between each exercise. At the end of the four-week intervention period, Patients A and B both requested that they continue on their exercise programs. Thus, data from a total of 8 weeks of supervised exercises were presented in these case studies.

Patients C and D received instruction in a Home Exercise Program prior to hospital discharge in accordance with the current standard of care for post-BMT patients at M.D. Anderson Cancer Center. This standard of care consists of a multi-disciplinary educational session in which patients receive instruction from nurses, social workers and physical therapists or physical therapist assistants. The physical therapist or assistant educates the patients in a home program that is primarily a walking regimen. Patients also received education on the importance of staying active through general physical activity (i.e., walking) and performing as much of one's activities of daily living as possible. They were also instructed about exercise safety and infection control considerations. Printed copies of these instructions were provided to the patients.

Tables 3.1 and 3.2 list the biweekly exercise logs for Patients A and B. The values on the Table are the highest values achieved for that period. Over the exercise period, the speed/time on the treadmill or bike was gradually lengthened; by the eighth week, the patients were walking or biking continuously for 30 minutes on the treadmill, at a moderate pace. Likewise, resistance on the upper and lower extremity exercises was gradually increased once the patients were able to easily complete 10 – 12 repetitions. The two patients had similar but not identical exercise programs. The patients' blood counts were monitored throughout the 8 weeks of exercise. If hemoglobin counts fell below 8.0 g/dL, or if the patients were judged by their physicians to need a blood product transfusion, then the exercise session was postponed or re-scheduled.

Table 3.1 Exercise log for Patient A

	First session	Week 2	Week 4	Week 6	Week 8
Treadmill	2.2 mph, 10 min., 0% incline	2.5 mph, 15 min., 0% incline	3.0 mph, 20 min., 2% incline	3.0 mph, 20 min., 3% incline	3.2 mph, 30 min., 5% incline
Bicycle ergometer	2.0 mph, 10 min.	3.0 mph, 15 min.	15 min., variable speed (pre-set interval course)	15 min., variable speed (pre-set interval course)	15 min., variable speed (pre-set interval course)
Total Gym squats	Level 6, 44 lbs., 10 reps, 3 sets	Level 6, 44 lbs., 12 reps, 3 sets	Level 7, 50 lbs., 12 reps, 3 sets	Level 7, 50 lbs., 15 reps, 3 sets	Level 8, 60 lbs., 15 reps, 3 sets
Total Gym heel raises	Level 6, 44 lbs., 10 reps, 3 sets	Level 6, 44 lbs., 12 reps, 3 sets	Level 7, 50 lbs., 12 reps, 3 sets	Level 7, 50 lbs., 15 reps, 3 sets	Level 8, 60 lbs., 15 reps, 3 sets
Cybex leg press	25 lbs., 10 reps. 3 sets	30 lbs., 12 reps. 3 sets	35 lbs., 12 reps. 3 sets	35 lbs., 15 reps. 3 sets	40 lbs., 15 reps. 3 sets
Cybex knee extension	10 lbs., 10 reps, 3 sets	10 lbs., 10 reps, 3 sets	10 lbs., 12 reps, 3 sets	10 lbs., 15 reps, 3 sets	10 lbs., 15 reps, 3 sets
Cybex lat pulldowns	10 lbs., 10 reps, 3 sets	15 lbs., 10 reps, 3 sets	15 lbs., 12 reps, 3 sets	15 lbs., 15 reps, 3 sets	15 lbs., 15 reps, 3 sets
Cybex bicep curls	10 lbs., 10 reps, 3 sets	10 lbs., 10 reps, 3 sets	10 lbs., 12 reps, 3 sets	10 lbs., 15 reps, 3 sets	10 lbs., 15 reps, 3 sets
Stairs	Up and down 20 steps, 1 lap	Up and down 20 steps, 3 laps	Up and down 20 steps, 5 laps		

Table 3.2 Exercise log for Patient B

	First session	Week 2	Week 4	Week 6	Week 8
Bicycle ergometer	2.0 mph, 10 min.	3.0 mph, 12 min.	4.0 mph, 15 min.	4.0 mph, 15 min.	15 min., variable speed (pre-set interval course)
Upper extremity bicycle ergometer	2.0 mph, 10 min.	2.0 mph, 12 min.	2.0 mph, 14 min.	2.0 mph, 15 min.	2.0 mph, 15 min.
Cybex leg press	40 lbs., 10 reps, 3 sets	40 lbs., 10 reps, 3 sets	45 lbs., 10 reps, 3 sets	50 lbs., 12 reps, 3 sets	50 lbs., 12 reps, 3 sets
Cybex knee extension	10 lbs., 10 reps, 3 sets	10 lbs., 10 reps, 3 sets	10 lbs., 12 reps, 3 sets	10 lbs., 12 reps, 3 sets	15 lbs., 12 reps, 3 sets
Cybex hamstring curls	10 lbs., 10 reps, 3 sets	10 lbs., 10 reps, 3 sets	10 lbs., 12 reps, 3 sets	10 lbs., 12 reps, 3 sets	15 lbs., 12 reps, 3 sets
Cybex lat pulldowns	15 lbs., 10 reps, 3 sets	15 lbs., 10 reps, 3 sets	20 lbs., 10 reps, 3 sets	25 lbs., 12 reps, 3 sets	30 lbs., 12 reps, 3 sets
Cybex bench press		15 lbs., 10 reps, 3 sets	15 lbs., 10 reps, 3 sets	15 lbs., 12 reps, 3 sets	15 lbs., 12 reps, 3 sets
Cybex bicep curls	7 lbs., 10 reps, 3 sets	7 lbs., 10 reps, 3 sets	7 lbs., 10 reps, 3 sets	7 lbs., 12 reps, 3 sets	10 lbs., 12 reps, 3 sets
Stairs	Up and down 20 steps, 2 laps	Up and down 20 steps, 3 laps	Up and down 20 steps, 5 laps		

Outcomes/ Results

Patients A and B, who participated in the supervised exercise program, were able to attend 18 and 19 sessions, respectively, out of a total of 24 possible sessions over the eight week period. The sessions missed were due to low blood counts necessitating a blood transfusion, or due to other medical appointments. With the exception of the sessions missed due to low blood counts, the patients' hemoglobin counts for the 8 week period ranged from a low of 9.0 g/dl to a high of 10.5 g/dl. Both patients were generally motivated and performed the exercises without any increase in symptoms (i.e., fatigue, nausea, etc.). Rest periods during the exercise sessions gradually decreased in frequency and duration over time. Patients C and D, who participated in non-supervised exercise, reported that they kept active by means of walking and keeping busy with household chores. Both of these patients, who were from out of town, also participated in several social activities (e.g., shopping, going to the movies, dining out, etc.) particularly when their children came to visit them. During the course of the 8 weeks of follow-up, these patients' hemoglobin counts ranged from 9.8 g/dl to 11.2 g/dl.

The physical performance measures from baseline, 4 weeks, 8 weeks are presented in Table 4. The values obtained in the physical performance tests at baseline for all 4 patients were all well below the reported values for healthy adults.[135, 170] After eight weeks, improved times and distances from baseline evaluation were noted in most of the physical performance measures. In all of the performance measures, at least one of the patients performed at par with healthy adults. They show a gradual improvement for most of the measures over time. The time for the repeated sit-to-stand test at the end of eight weeks was superior to the baseline by more than a second for all of the patients (range: 1 -

3.53 seconds improvement). All patients had improved times in the 50 foot walk, with the exception of 1 patient (Patient D) who had slightly slower times during both the 4 and 8 week re-evaluations compared with baseline. For the 6-minute walk, 3 of the patients covered a longer distance after 4 weeks but had a decrease in distance walked at the 8-week re-evaluation compared with the 4-week re-evaluation. Distance reached in the forward reach test stayed relatively the same over the 4 and 8 week re-evaluation. Generally, there was a more substantial improvement in physical performance after the first four weeks, and a lesser degree of improvement from the fourth to the eighth week. Figures 2 – 5 shows how each of the patients performed on each of the physical performance measures for each patient. All of the patients improved over the 8-week period; the 2 patients who participated in the supervised exercises generally showed a steadier improvement in the physical performance measures, while the 2 patients who participated in non-supervised exercise had relatively smaller improvements or even slight declines in performance, such as in the 6-minute walk.

Table 4. Physical performance measures at baseline, 4 weeks, and 8 weeks

		Baseline	4 weeks	8 weeks	Healthy adults[135]
Sit to stand (sec.)	Patient A	4.37	3.62	3.41	2.46 ± 1.18
	Patient B	5.44	4.03	1.91	
	Patient C	4.44	3.41	3.16	
	Patient D	3.96	2.38	2.28	
50 foot walk (sec.)	Patient A	9.75	8.96	8.90	8.87 ± 1.93
	Patient B	9.32	8.63	7.78	
	Patient C	8.34	7.58	8.00	
	Patient D	10.33	10.78	10.89	
6 min. walk (m.)	Patient A	379.17	531.27	499.26	556 ± 90.61
	Patient B	315.16	471.22	532.49	
	Patient C	515.11	540.11	495.60	
	Patient D	396.85	415.75	396.24	
Forward reach (cm)	Patient A	34.0	36.0	36.3	38.76 ± 8.09
	Patient B	40.1	38.2	38	
	Patient C	41.0	42	38.5	
	Patient D	39	39.5	39.5	

Figure 2. Repeated sit-to-stand test for each subject at baseline, 4 weeks, and 8 weeks

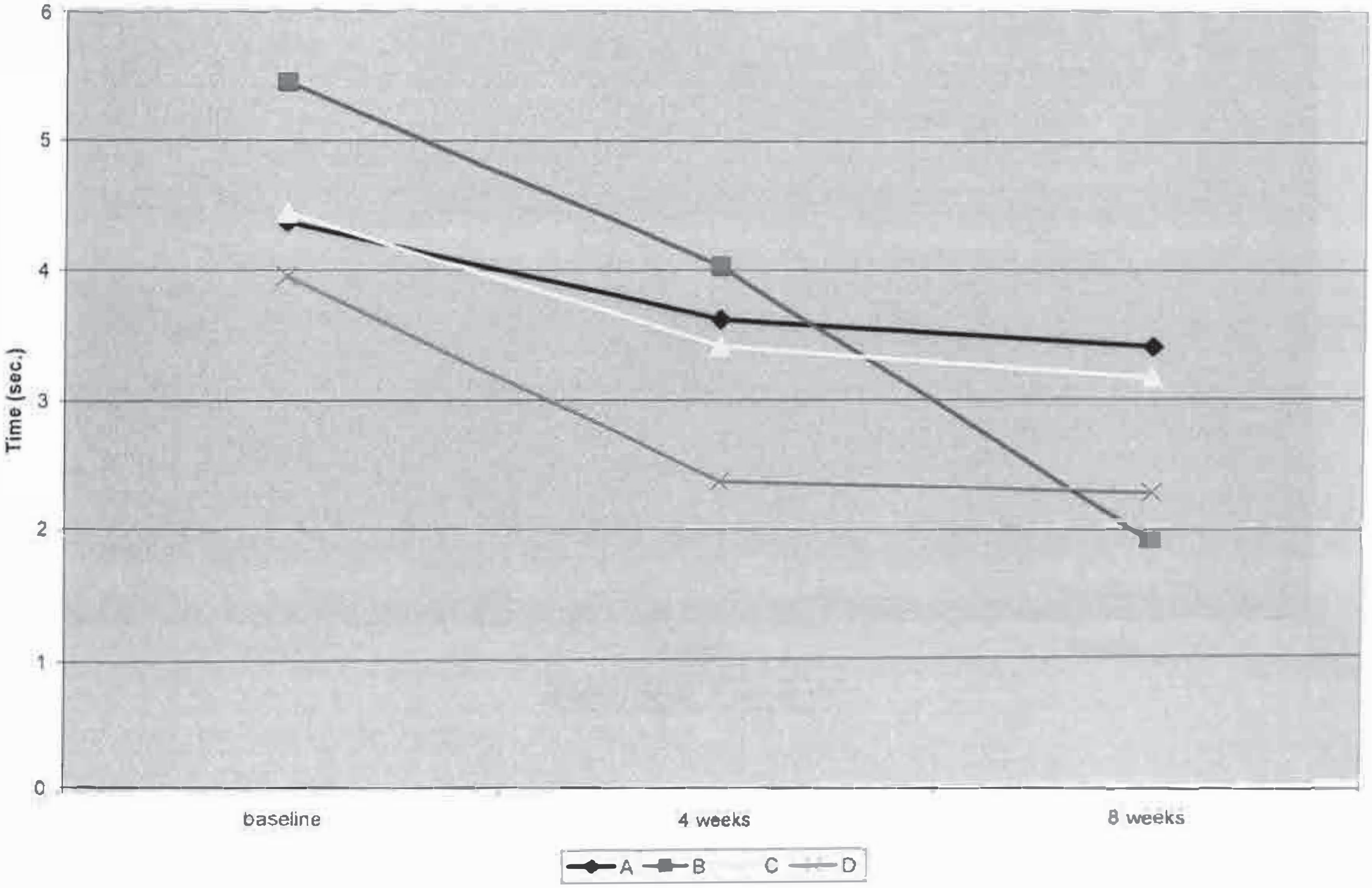


Figure 3. 50-foot walk for each subject at baseline, 4 weeks, and 8 weeks

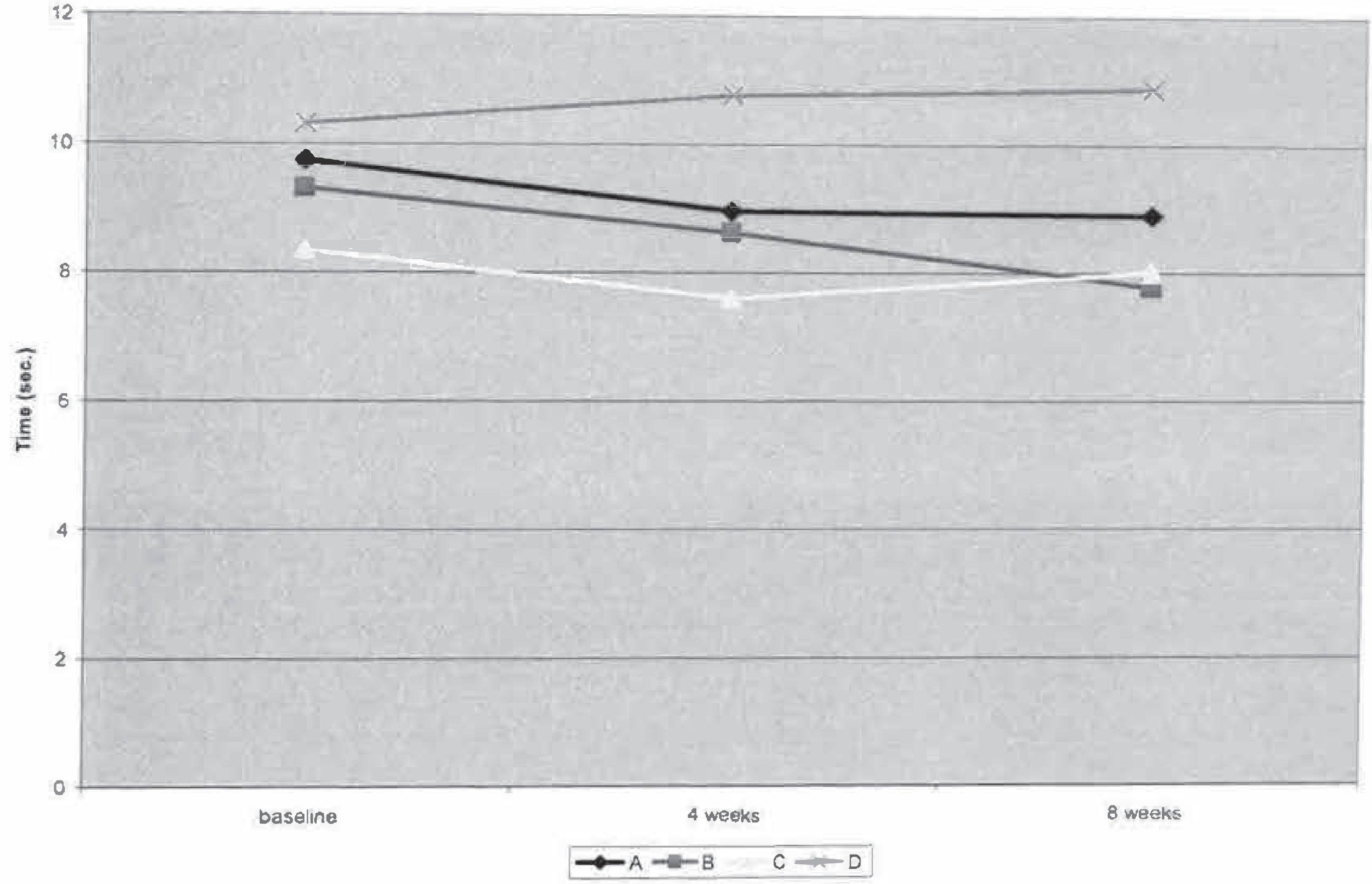


Figure 4. 6-minute walk for each subject at baseline, 4 weeks, and 8 weeks

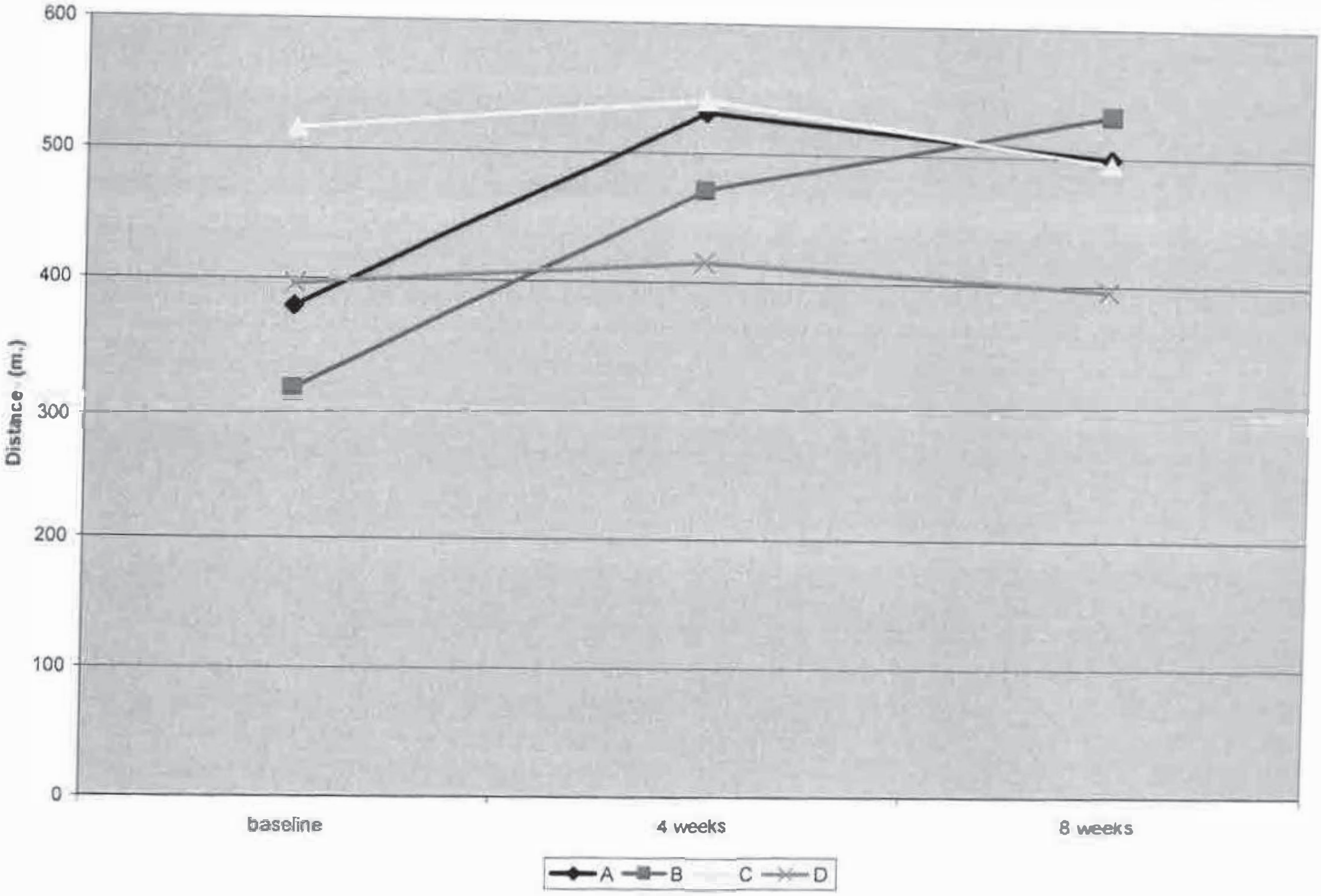


Figure 5. Forward reach for each subject at baseline, 4 weeks, and 8 weeks

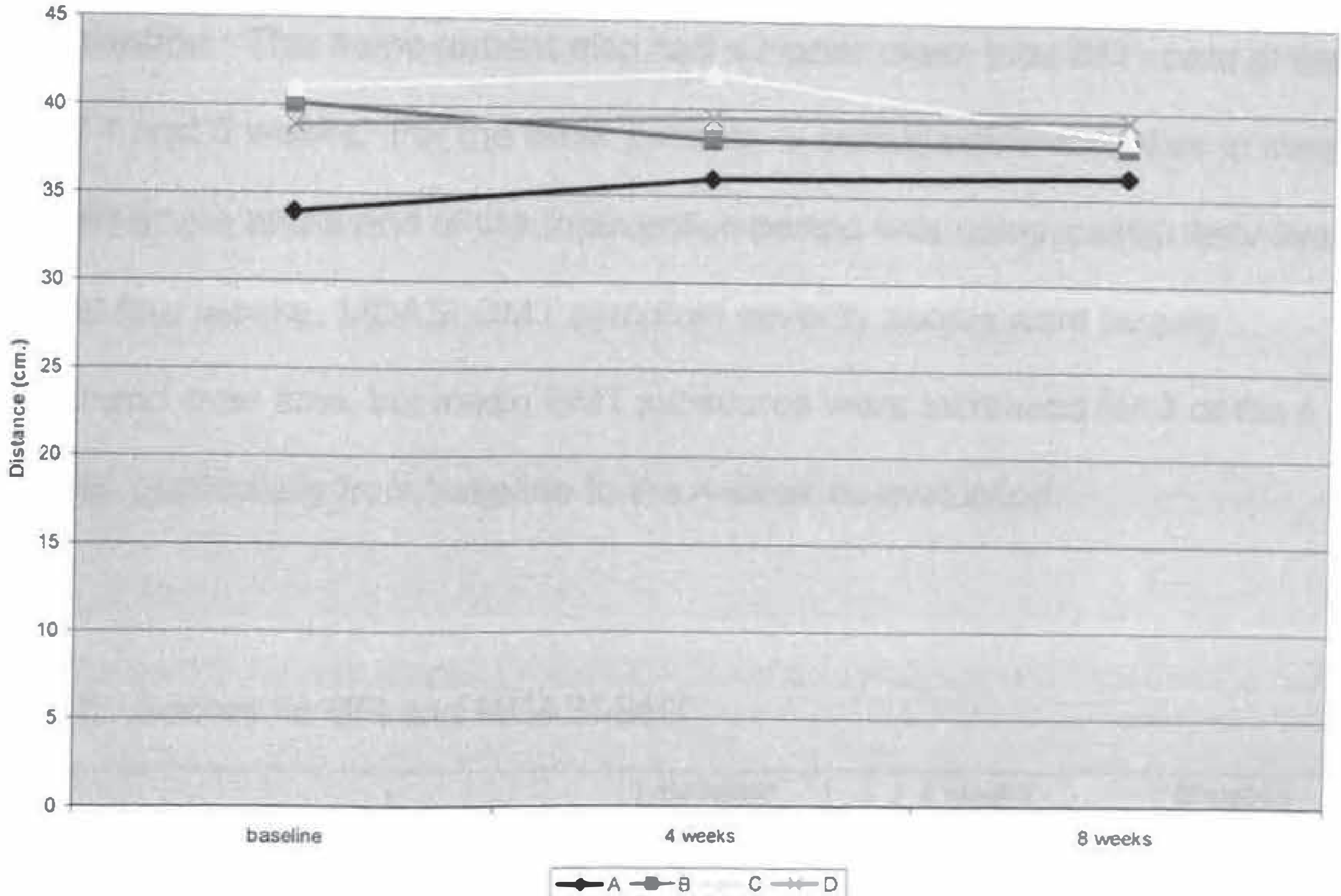


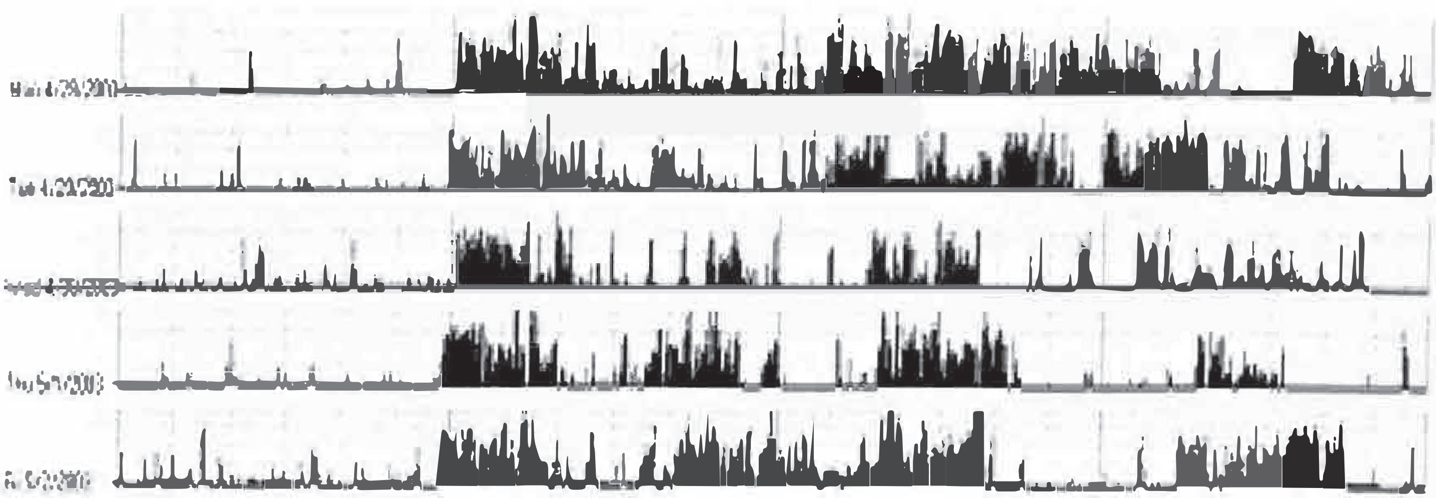
Table 5 shows the BFI and MDASI-BMT scores. With the BFI, fatigue severity, measured by the item "worst level of fatigue" is considered severe with a score of 7 or higher the 0-10 scale. A score of 1-3 is considered "mild" 4-6, "moderate" and 7-10 "severe".[139] Thus, the patients had moderate to severe levels of fatigue initially. However, fatigue severity showed a steady decline over time, with the exception of Patient C who reported a decrease in fatigue severity at the 4-week re-evaluation but had an increase in fatigue severity at the 8-week re-evaluation. This same patient also had a higher mean total BFI score at the end of 4 and 8 weeks. For the other patients, a considerable decrease in mean total BFI score at the end of the intervention period was noted, particularly over the first four weeks. MDASI-BMT symptom severity scores were largely unchanged over time, but mean BMT subscores were increased for 3 of the 4 patients, particularly from baseline to the 4-week re-evaluation.

Table 5. Scores for BFI and MDASI-BMT

		Baseline	4 weeks	8 weeks
Worst fatigue (0-10)	Patient A	8	6	5
	Patient B	5	4	4
	Patient C	5	4	8
	Patient D	10	9	8
Mean BFI score (0-10)	Patient A	2.67	1.78	2.33
	Patient B	4.78	2.44	2.33
	Patient C	.78	2.78	5.22
	Patient D	5.89	3.77	2.44
MDASI-BMT symptom severity score (0-10)	Patient A	.61	.58	.89
	Patient B	1.37	1.21	.79
	Patient C	.26	1.00	2.00
	Patient D	3.68	4.58	5.37
MDASI-BMT BMT subset score (0-10)	Patient A	1.00	4.00	4.00
	Patient B	1.67	4.00	2.00
	Patient C	1.17	7.00	9.00
	Patient D	2.50	2.33	2.33

All the patients reported no difficulty wearing the wrist activity monitor. The patients followed conventional diurnal cycles for the most part, getting out of bed between 6 – 10 a.m. and returning to bed between 9 p.m. and 1 a.m. Actigraph data revealed numerous night awakenings for all the patients. Night awakenings ranged from 6.33 – 81.18 minutes, and increased in frequency during the eighth week compared to the first. The subjects reported that awakenings were primarily for urination or discomfort. There was also several sleep episodes noted throughout the daytime for all of the patients, mostly in the late afternoons. Sleep duration over 24 hours ranged from 7.17 to 14.67 hours during the first week, and 8.36 to13.8 hours during the eighth week. Total activity counts in the PIM mode increased over the eight week period, from a mean of 5108.42 during the first week to 6579.84 during the eighth week. With graphical analysis, activity counts were higher and more sustained on days the patients reported to be exercise days. The acceleration index represents the change in activity rate during a 24-hour interval, with a negative value representing slowing during the interval, and a positive value representing acceleration. The acceleration index for the patients was a mean of 0.10 during the first week and 0.09 during the eighth week. The activity index, or percentage of epochs with an activity score greater than 0 score, showed a gradual increase from first to eighth week, from 63.31% during the first week to 80.56% during the eighth week. Figure 6 is an example actigraph tracing showing sleep and wake episodes. Each bar of the histogram represents the total deviation from zero volts in one minute.

Figure 6. Sample actigraph sleep and wake readings for 1 patient. Sleep episodes are in red.



Discussion

Although allogeneic BMTs were once salvage procedures for patients with resistant and end stage malignancies, they are now generally performed earlier in the disease course, due to improved understanding and management of complications, new pharmacological agents and broadening of the eligibility criteria for transplantation. Despite this, many allogeneic BMT patients have difficulty with physical function or day-to-day task performance. It thus makes sense to evaluate these patients using functionally-based measures of physical performance. Much of previous research on the effects of exercise on BMT patients has focused on objective physiologic outcomes (e.g., cardiac function, hematological indices, or muscle performance) and/or psychological outcomes (e.g. depression or mood).[20-22, 84] Although these studies have provided important information, they may not provide a complete picture of the changes in function resulting from exercise.

As shown in Figs. 2-5, our patients from this small case series show an improvement in most of the physical performance tests, whether our subjects engaged in supervised exercise or non-supervised exercise. The patients who participated in supervised exercise, though, did have relatively greater net gains across the performance tests. While the patients' range of motion and muscle strength were deemed good and they did not complain of any major functional limitation, their disease and treatment could have caused subclinical changes in motor function. Generally, more substantial improvements were observed after the first four weeks than the second four weeks, though the increase in supervised and non-supervised exercise intensity and progressions were of a very gradual nature over the 8-week period. The relatively larger improvements earlier on could be partly due to the patients being fairly sedentary before starting the exercise program, and accordingly, gains were seen fairly quickly.

The patients were very receptive to the exercises and considered them important elements of their recovery. Patients A and B, who took part in a supervised exercise program, both reported that they appreciated that there was someone knowledgeable who could help them, motivate them, and provide them with feedback. The exercises were deemed sufficiently challenging; they felt "tired, but in a good way." There were isolated incidents when the close supervision of the therapist proved to be "a little tiring." On the other hand, Patients C and D both liked the fact that they could exercise at their own pace and time. However, both also stated that there were numerous occasions when they were too fatigued or not motivated enough to engage in physical activity, and therefore failed to exercise as regularly as they would have liked. In these instances, as Patient D notes, "someone to encourage me to exercise might have been helpful." Unfortunately, neither of the patients who engaged in non-supervised exercise was able to complete detailed exercise diaries. Although Patients C and D report they wore their actigraphs during exercise days, they sometimes could not recall with certainty what times they exercised.

Both of the patients who participated in supervised exercise missed more exercise sessions during the second four weeks than during the first four weeks. Similarly, both of the patients who were exercising in a non-supervised fashion also reported that they were not able to exercise as regularly during the second 4 weeks compared to the first 4 weeks of follow-up. Reasons given for not being able to exercise included feeling too tired or not being motivated. The patients' less regular exercise frequency might be attributed to the appearance of transplant-related complications during this second 4-week period. Diez-Campelo and colleagues [143] previously noted the appearance of acute GVHD complications at a median of 35 days (range: 10-125 days) post-allogeneic transplant. In this case series, during the second 4-week follow-up period, Patients A and B had to have a number of blood transfusions due to low blood counts. Patient C had a very persistent pruritic rash all over his trunk and extremities, and Patient D complained of increasingly blurred vision due to CMV retinitis that made it a bit difficult for her to exercise regularly.

All of the patients walked a longer distance in the 6-minute walk test, which is a measure of endurance, and had faster times in the repeated sit to stand, which is a measure of strength. The supervised exercise program was primarily of an aerobic nature, supplemented by resistance exercises, so it makes sense that gains were made in those areas. The unsupervised exercises consisted of a walking regimen. The patients performing non-supervised exercises, while having considerable gains in the 6 minute walk test during the 4-week re-evaluation, actually slipped to slightly below baseline levels in the 8-week follow-up. This could be attributed to the appearance of acute GVHD symptoms that may have bothered the patients during the performance of activities that take a longer period of time to complete. Interestingly though, they had faster times in the repeated sit to stand test and 50 foot walk. Perhaps because they were fairly sedentary at the outset of the program, any type of physical activity may have resulted in gains. Also, these activities took less time to complete and did not really need as much sustained levels of exertion. Dimeo and colleagues have reported increases in walking speed using a treadmill stress test among autologous transplant patients after participation in a supervised exercise program.[21] The smallest gains were observed in the forward reach test, which is a measure of balance. Our patients did not have significant problems with balance at the initiation of the exercise program, and balance was not an issue throughout the 8 weeks.

All of our patients had some level of fatigue throughout the 8 weeks, but fatigue severity was lower at the end of 8 weeks compared to baseline. Fluctuations in fatigue severity may be related to hematologic indices; the patients' blood counts, particularly the hemoglobin levels, were monitored regularly. These values, though lower than normal,[168] were relatively stable. Decreases in fatigue severity corresponded to increases in physical performance, particularly in the baseline to 4-week period. Reduction in fatigue levels has been a consistent finding in studies examining exercise in many types of cancer diagnoses.[9, 10, 146] While these improvements may be due to the patients' improved functional capacity, they may also point to the patients' improved abilities to manage their fatigue. The total BFI score was much lower than fatigue severity. This pattern of BFI values, higher fatigue severity values and lower total scores is similar to the BFI values reported by Simmonds with a mixed cancer diagnosis sample.[135] The discrepancy in scores is probably due to the fact that the total score is a mean value that could be influenced by the "0"s reported for such items as "fatigue interferes with mood" or "fatigue interferes with relationships with other people."

Generally, the patients' mean total MDASI-BMT scores were not very high (≈1/10) throughout the 8 weeks. The exception was Patient D, whose scores were higher after 8 weeks; however, this increase was due to increased sleep disturbance and fatigue, as well as feelings of distress and sadness at that time. When asked about it, she reported that it was secondary to some conflict within the family. BMT-related symptoms such as mouth sores, diarrhea, and concentrating were not major issues for our patients, with the exception of Patient C, who reported oral problems and a persistent skin rash consistent with acute GVHD.

Actigraphs are a way of quantifying a person's activity patterns throughout the day. There is very little information on the activity levels or quality of sleep in BMT patients, given that these patients often report disturbed sleep and decreased vigor. Historically, actigraphs have been used to provide objective data for sleep disorders. However recently, they have begun to be used for the assessment of rest and movement patterns as well.

The use of actigraphs in oncology patients is even more recent, with almost all published studies occurring in the past 10 years. Miaskowski and Lee,[123] using wrist actigraphs to monitor the activities of outpatients undergoing radiation therapy over a 48-hour period, reported that the actigraphs were valid and objective measures of sleep efficiency in this population. Other studies using actigraphs have shown fluctuating patterns of lowered activity and disturbed sleep in cancer patients receiving either chemotherapy [130] or radiation therapy.[131] Disturbances in rest/activity rhythms were also linked to lower functional scores and higher symptom scores on quality of life questionnaires.[132]

Patients complained of not being able to sleep well; objective actigraph data showed them waking an average of 16 times during the night. Fragmented sleep episodes have also been reported in a mixed cancer cohort likewise participating in an exercise program (mean = 14 night awakenings).[15] Many of our patients' night awakenings were of fairly short duration ($\approx$ 10 min.), but they had an unfavorable effect on the patients' sleep efficiency. Frequent urination, cited by our patients as a common cause of awakening at night, was also reported as the most common cause of awakenings in hospitalized BMT patients.[171] Patients had, on average, slept about 11 hours throughout the 8 week monitoring period; however, fatigue severity was still moderate to severe. However, even with a moderate level of fatigue and increased sleep disturbance, the patients who performed supervised or unsupervised exercise still scored better on most of the physical performance tests. At the very least, physical performance was comparable to pre-intervention levels. This result is similar to findings reported by Dimeo and colleagues [20, 24] with autologous transplant patients where those who exercised improved or at least maintained physical performance on a submaximal treadmill stress test. In contrast, patients who did not train actually suffered declines in physical function.[20]

Activity counts were usually higher on the days that the patients exercised. For the patients in the supervised exercise program, the upper extremity exercises they performed probably contributed to the higher activity counts, but it should be noted that activity levels also usually remained sustained throughout those days (i.e., not much change in activity levels throughout the day). There typically would be an initial burst of activity upon waking up in the morning, which probably corresponded to the patients getting ready to go the Ambulatory Treatment Center. There might be another increase in activity count during late mornings, either because the patients were in the Rehabilitation Services Department for their exercise sessions, or they were walking around the Ambulatory Treatment Center getting in their exercise or socializing with other patients. Otherwise, lower activity counts or sleep episodes would be observed corresponding to the patient resting in bed waiting for medical treatment. There was often another burst of activity in early afternoon before tapering off during the evenings. Periods of lowered activity, which could be attributable to naps or rest periods, were frequently noted during most afternoons or early evenings. This was particularly true in Patient D's case, whose fatigue severity remained severe, and numerous sleep episodes were seen throughout the day, mostly during late afternoon/early evening. Napping has been used by oncologic patients as a strategy to reduce fatigue.[123]

It cannot be conclusively inferred from this case report that exercise, whether supervised or non-supervised, directly affected the gains observed in physical performance and fatigue severity. The patients had not received any other therapeutic intervention during the duration of this case series, which suggests a link between exercise and the reported improvements. However, other factors could have affected the outcomes, such as the timing of the patients' various medications following the allogeneic BMT, or the attention the patients received during the duration of this case series, or the patients learning to manage their fatigue and other symptoms more effectively. This is a small case series, and the findings here may not be representative of the larger population of recent post-allogeneic transplant patients. It would also have been beneficial if the patients who were performing non-supervised exercise had kept a more detailed exercise log detailing frequency, duration, and type of exercise. Though those patients had been instructed to keep an exercise log, both of them failed to keep up-to-date logs. In addition, it is unknown what magnitude of change in the outcomes would be considered a successful intervention. Some features of the actigraph used in this case series are subject to individual interpretation; the tracings in themselves only show activity frequency and intensity, and does not tell what specific activities the wearer is engaged in, or distinguish between similar activities of differing difficulty level (e.g., walking uphill versus walking on level ground). Further studies examining these issues would help to clarify the role of exercise following recent allogeneic BMT.

Conclusion

This case series describes the outcomes of four patients who participated in an 8-week outpatient exercise program after recent allogeneic BMT. The exercises were of either a supervised or a non-supervised nature. These exercises were safe and well tolerated by the patients. Improvements were seen in strength, walking speed, and endurance, as well as fatigue severity. However, these gains were more pronounced after the first 4 weeks, and in the patients who had participated in supervised exercise. Although irregular sleep and wake patterns were observed, activity frequency and intensity were enhanced, suggesting better physical function and/or fatigue management. This case series illustrates the value of exercise in ameliorating physical decline following recent allogeneic BMT.

CHAPTER VI

SUMMARY

Favorable links between exercise and physical and psychological functioning in bone marrow/ peripheral blood stem cell transplant (BMT/PBSCT) patients have been a consistent finding in many recent studies. However, these studies have been largely performed with autologous BMT/PBSCT patients only. Given that allogeneic BMT/PBSCTs may give rise to numerous potentially detrimental sequalae, assessing the effects of exercise training in this population is important. In addition, because of the complex nature of cancer following BMT/PBSCT, there is a need to examine and compare different types of exercise regimens or conditions (i.e., supervised vs. unsupervised) to determine which is most beneficial to patients.

The aim of this study then were to perform an interim, exploratory examination describing the effect of short-term clinician-directed and self-directed exercise programs in recent allogeneic bone marrow transplant patients in terms of multi-dimensional outcomes. Other aims were to determine the influence and relationship of clinical and demographic variables on pre-treatment outcomes; to describe and compare activity and sleep patterns in post-

BMT/PBSCT patients using actigraphy; and to describe through a series of case reports changes in physical performance, activity patterns and quality of life during participation in a supervised or a self-directed exercise program.

In general, patients were very enthusiastic and accepting of both exercise regimens used in the study. However, subject recruitment was a major challenge in this study. As a result, and also because of marginal observed power for group differences, the clinician-directed and self-directed exercise groups were combined into a single group in many of the data analyses. Also, statistical tests of significance (i.e., two-way MANOVAs) were not performed for some analyses because data collection on a primary, larger study was still ongoing at the time of this analysis, and the study collaborators did not want to compromise the alpha significance level.

Within the short time period measured in this study, it appears that both clinician-directed and self-directed exercise regimens are beneficial for this group of patients and may result in improvements in physical performance and quality of life, and a reduction in fatigue severity. Significant relationships noted between self-reported measures point to the possible influence of fatigue and/or BMT-related symptomatology on quality of life, particularly its physical and functional aspects. Fatigue and altered activity and sleep patterns were significant problems among the subjects. Polyphasic activity patterns, with longer than normal sleep durations and shorter than normal sleep episode lengths were observed via actigraphy. A number of night awakenings were also noted. Improvements, though non-statistically significant, were noted in activity levels as was fatigue severity in subjects participating in both clinician-directed and self-directed exercise groups.

The presented findings must be viewed within the context of the study's limitations. The small sample size, coupled with the inability to conduct statistical tests of significance on part of the data due to ongoing data collection for the primary study, prevented a more comprehensive analysis of the results. The generalizability of these results is also then a consideration. It is unknown whether changes in the subjects' exercise and activity patterns occurred during the course of this study because the subjects could have discussed their exercise regimens with one another as most of them received their medical treatment or follow-ups in the same area of the hospital. Although improvements over time in physical performance, fatigue severity and quality of life are most likely due to participation in exercise, it is not entirely possible to rule out that some of the changes observed could be due to normal recuperative processes. Drawing conclusions from graphical analyses of actigraphy tracings is a cautious process. Tracings only depict activity frequency and intensity, but do not differentiate between similar activities of differing difficulty levels, for example, walking uphill versus walking on level ground.

Further research on the efficacy of different exercise regimens should be carried out on larger samples over a longer period of time, and to determine whether changes can continue to occur then (i.e., months or years after transplant) – especially with the potential development of chronic graft-versus-host disease in this population. It would also be beneficial to attempt to fine tune the dose of exercise that would most benefit the post-allogeneic transplant patient, as well as timing the start of the exercises to ameliorate the complex treatment-related side effects common in this patient population. An important question is what magnitude of change in the subjective and objective outcomes would comprise a successful intervention. As sleep disturbances and altered activity patterns seem to be a problem with these patients, additional research is needed to more clearly describe activity and sleep patterns using both objective and subjective measures. It would also be useful to investigate the correlates and/or predictors of disturbed sleep which would provide useful information for the development of interventions that may be helpful in managing this problem.

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APPENDIX A

Detailed Methods

Detailed Methods

Subjects

Forty-four patients agreed to participate in the study. The subjects were recruited from the Bone Marrow Transplant Service through the BMT clinic, Ambulatory Treatment Center (ATC), and the Department of Rehabilitation Services of the University of Texas – M.D. Anderson Cancer Center. These subjects were part of a larger series of studies examining outpatient rehabilitation interventions on the quality of life in patients following recent allogeneic bone marrow/ peripheral stem cell transplantation. Primary diagnoses were lymphoma or leukemia and subjects had undergone an allogeneic bone marrow or peripheral blood stem cell transplant within the last six months from the time of recruitment. They were receiving follow-up care in the Ambulatory Treatment Center and had been referred for Physical Therapy. Subjects were all ambulatory, although they were allowed to use an assistive device if necessary. Participants were able to perform most self-care activities independently, requiring no more than moderate assistance (no more than 50% assistance). Every effort was made to recruit from both genders, and from different racial and ethnic backgrounds.

Patients were excluded from the study if they were less than 17 years of age, or if they had a psychiatric diagnosis, significant cardiovascular disease, hemiplegia, or paraplegia. They were also excluded if they could not speak or understand English. Subjects were told that they could ask to be removed from the study if they chose to.

Measures

Physical Performance battery

The physical performance test battery (PPT) consists of a set of tasks in which the time taken to complete the task or the distance reached is measured. This series of tasks challenges physical function and also speed, endurance, and balance. Simmonds established the reliability, validity and clinical usefulness of this battery in patients with cancer.[135] There was excellent test-retest reliability ($r \geq 0.8$), all tasks had face validity, and they proved acceptable to the patients. In addition, the battery was found to be moderately responsive to change and a better predictor of disability than either impairment or psychosocial measures alone. Those tests that are part of the M.D. Anderson Cancer Center – Department of Rehabilitation Services standard patient evaluation were used in this study. The tasks are as follows:

- *50-foot walk at patient's fastest speed.* Subjects were timed as they walked a distance of 50 feet. They were told to walk as fast and as safely as they could.

- *6-minute walk*. Subjects walked as far, as fast and as safely as they could for six minutes while pushing a measuring wheel. The distance walked was then measured and recorded.
- *Forward reach*. Subjects stood next to a wall on which a meter stick had been mounted horizontally at shoulder height. The subjects stood next to the meter stick with their shoulder forward flexed to 90°, elbows extended, wrist at neutral and fingers extended. Keeping their heels on the floor, patients reached forward along the meter stick as far as they could. The distance reached was then measured and recorded in centimeters.
- *Timed repeated sit to stand.* Subjects sat on a flat surface, 18 inches in height. They were asked to rise to a standing position, without using their arms to push off, and return to a sitting position, as quickly and as safely as possible, twice.

Actigraphy

The Mini Motionlogger actigraph (Ambulatory Monitoring Inc., Ardsley, NY) is a compact, lightweight (1" diameter x .035" height, 14 g.) wrist or belt-worn unit that provides continuous monitoring of the patient's activity level. Figure 1 shows the Mini Motionlogger actigraph. The device has a non-volatile 32K memory with a 2-3 Hz bandwidth and 16 Hz sampling rate. Activity monitors have been found to be reliable in measuring total physical activity (ICC ranged from 0.65 - 0.91) in a cancer patient population and have adequate association with other measures of functional status.[124]

The actigraph was worn on the non-dominant wrist during the eight-week investigation period, except when bathing or swimming. Relatively high correlations exist between wrist, trunk and ankle movements (r = .76 - .81), and activity measurements between the dominant and non-dominant wrists have been found to be comparable.[128, 161] The actigraphs were initialized using the Actigraph Interface to begin recording at 1700 h on the day the actigraph was issued to the subject. Activity level was measured in one minute epochs, and activity data collected in the Proportional Integrating Mode (PIM) mode of operation. The PIM measures movement intensity by summing the deviations from zero volts, i.e., the absolute value of the voltage, each 0.1 second during the epoch and storing the value at the end of each epoch. Each epoch (time frame recorded by the actigraph) is one minute. Figure 2 illustrates the PIM mode.

Data collected by the actigraph was downloaded to a computer via the

Interface unit and ACT computer software (Ambulatory Monitoring Inc., Ardsley, NY). The ActionW software (Ambulatory Monitoring Inc., Ardsley, NY) was used to score sleep and wake activities, plot linear actigrams, and calculate summary statistics. Sampling over the course of at least five continuous days monitoring is sufficient to obtain at least 80% reliability.[129]

Figure 3 illustrates an example of the linear actigram produced by the ActionW software. This was a recording done on one cancer patient. The patient performed a 6-minute walk, followed by a 10-minute rest period; a 2-minute seated belt tie, followed by a rest period; and 2 minutes of getting in and out of a chair. The actigraph was worn on the non-dominant wrist. Each bar of the histogram represents the total deviation from zero volts in one minute – the higher the bar, the more vigorous or higher the activity level. Thus, higher intensity activities (e.g., walking) are represented by the higher bars, and periods of rest or lower intensity activity (e.g. rest periods, belt tie) by the lower bars.

Figure 1: Mini Motionlogger actigraph

Figure 2: The area in blue represents the PIM mode. The area under the curve is a measure of activity level or intensity.

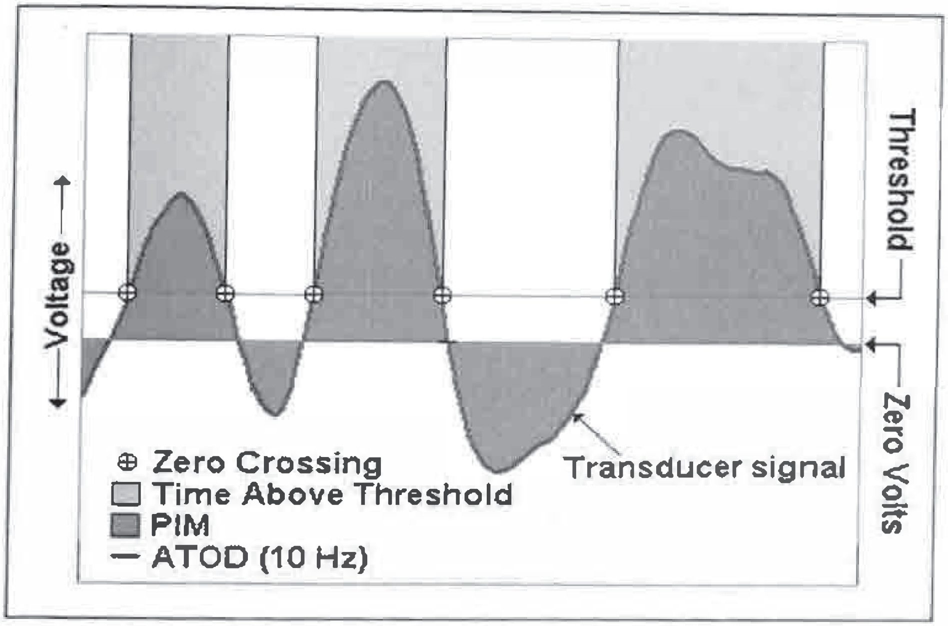
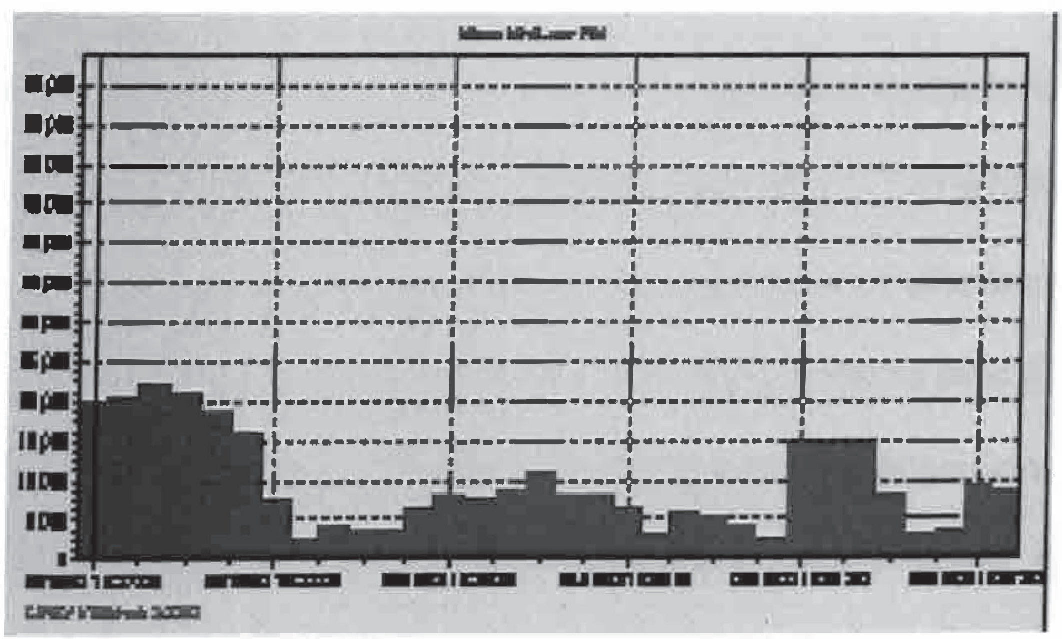


Figure 3. Actigraph record provided by ActionW software with actigraph worn on wrist.



Self-reports

Brief Fatigue Inventory (BFI): a self-administered assessment of fatigue severity. The BFI characterizes the presence and impact of fatigue on function; its reliability and validity have been established in patients with cancer.[139] It consists of 9 items measured on a numeric scale from 0-10, with 0 being "no fatigue" or "fatigue does not interfere" and 10 being "fatigue as bad as you can imagine" or "fatigue completely interferes". Higher scores indicate higher levels of fatigue and greater interference of activity.

M.D. Anderson Symptom Inventory – BMT (MDASI-BMT): a brief measure of the severity and impact of cancer-related symptoms. The core MDASI measures 13 cancer-related symptoms and 6 items describing how much symptoms interfered with different aspects of the patient's life in the last 24 hours. Both the symptom scales and symptom interference scales of the MDASI exhibited high internal consistency ($\alpha \geq .82$).[140] In addition, the MDASI was highly correlated with independent indicators of disease and treatment severity. The BMT module contains the core MDASI items plus 6 additional symptoms identified as problem areas by transplantation physicians and nurses. These additional symptoms include: weakness, mouth sores, diarrhea, feeling physically sick, difficulty paying attention, and bleeding. This subscale is currently undergoing psychometric testing.

Functional Assessment of Cancer Therapy – Bone Marrow Transplant (FACT-BMT): a measure of quality of life in bone marrow transplant patients. The FACT–BMT (version 4) is composed of the FACT–General, that addresses general health-related quality of life for cancer patients, with the addition of a 23-item Bone Marrow Transplant subscale (BMTS), that addresses issues specific to bone marrow transplant patients. The FACT-G contains subscales relating to Physical Well-Being, Social/Family Well-Being, Emotional Well-Being, and Functional Well-Being. Each item on the FACT-BMT consists of a 5-point categorical scale, with answers ranging from 0 (not at all) to 4 (very much), that applies to the previous seven days. It provides a total score for overall quality of life and subscale scores. Coefficients of reliability and validity ranged from 0.86 to 0.89 for the entire FACT-BMT and 0.54 to 0.63 for the BMTS. The BMTS was able to discriminate patients on the basis of performance status rating and also demonstrated sensitivity to change over time.[141]

Self-efficacy scale: a measure that is designed to tap subjects' perceived capability to exercise three times per week over a specified period of time in the face of commonly identified barriers to participation. Participants indicate their degree of confidence for each item on a 0% (no confidence at all) to 100% (completely confident) scale. The confidence scores are then summed and divided by the total number of items giving a possible range of 0 – 100%--a higher number indicates a greater degree of confidence. The scale also asks the patient to indicate (yes or no) whether commonly identified barriers get in the way of exercise and whether these barriers are overcome by the participant. Self-efficacy has been found to significantly predict exercise behavior when biological influences (e.g., gender, body composition) and behavioral influences (i.e., past exercise frequency) are controlled.[172, 173]

Global perception of change: a one-item question that seeks the patient's perception of change in their overall condition since the beginning of the study period. It consists of a numerical scale on perceived magnitude of change from -7 (a very great deal worse) to 7 (improved a very great deal), and perceived importance of change from -7 [change (better or worse) is not at all important] to 7 [change (better or worse) is very important].

Procedure

Subjects who met the inclusion criteria and who agreed to participate signed an informed consent form. After being evaluated by a physical therapist, they were randomly assigned to a clinician-directed supervised exercise group or to a self-directed, self-paced unsupervised exercise group. Random assignment was done through the University of Texas – M.D. Anderson Cancer Center Patient Data Management System (PDMS).

Subjects in the self-directed exercise group received instruction on a Home Exercise Program according to the current standard of care for post-BMT patients at M.D. Anderson Cancer Center. This standard of care consists of a multi-disciplinary educational session in which patients receive instruction from nurses, social workers and physical therapists or physical therapist assistants. The physical therapist or assistant educated the patients on home exercises consisting mainly of a walking regimen. Patients also received education on the importance of staying active through general physical activity (i.e., walking) and performing as much of one's activities of daily living was emphasized. They were also instructed about steroid myopathy and peripheral neuropathy; exercise safety; and infection control considerations. The education session with the physical therapist or physical therapist assistant lasted approximately 30 – 45 minutes. Printed copies of these instructions were provided to the patients.

Subjects in the clinician-directed exercise group participated in a structured exercise program. These exercises were performed in the Rehabilitation Services gym under the supervision of a physical therapist and physical therapy assistant. This exercise program was tailored to the patient's needs and included aerobic exercises, resistive exercises (free weights and machines), and walking on a treadmill or biking on an ergometer. Each exercise session lasted approximately 45-60 minutes, thrice weekly, with at least 20 – 30 minutes comprising aerobic exercises, and the rest of the time comprising resistance exercises. The sessions were scheduled to coincide with the patient's scheduled visits to the Ambulatory Treatment Center for intravenous fluids or medical monitoring. This was done to encourage the patient to attend the exercise sessions, as she would not have to schedule a special trip to the facility. The entire exercise program lasted four weeks. Subjects in the self-directed exercise group were offered the opportunity to take part in a clinician-directed exercise program at the end point of the study.

All participants were evaluated at baseline and four weeks, with a longer-term follow-up at 8 weeks post-recruitment. All testing was done at the Rehabilitation Services Department of M.D. Anderson Cancer Center. During baseline evaluation, subjects were asked to complete the self-report questionnaires as well as the physical performance test battery. A physical therapist or physical therapist assistant trained in the administration of the performance task battery, and blinded as to group assignment directed the execution of the task battery for all subjects. For each of the timed performance tasks, the patients were instructed to perform the tasks as safely and as quickly as they could. For the forward reach task and the 6-minute walk, they were asked to reach or walk as safely and as far as they could, respectively. The testing order of the performance tasks was done randomly, except for the 6-

minute walk, which was always performed last. Subjects were advised that they could rest between each task. They were also reminded that they could refuse to perform or complete any task if they wish without prejudice to them. The entire evaluation took approximately 30 – 60 minutes. At the end of four weeks, all subjects once again completed the self-report questionnaires and physical performance battery. In addition, they were asked about their Global Perception of Change. At the end of 8 weeks, subjects completed all of the baseline instruments and the Global Perception of Change. Participants were contacted by telephone or visited at the ATC to remind them of the follow-up evaluations.

A subgroup of ten (10) participants – 20 total participants – from both the clinician-directed and self-directed exercise groups was randomly selected through the PDMS system to use the actigraphs. The actigraphs were introduced to these participants during baseline evaluation. They were instructed on its use, including a demonstration of how it works. They were asked to wear the actigraphs continuously over the first four weeks of the study period. The actigraph was initialized to begin recording at 1700 h on the day the actigraph was issued to the participant. At the end of two weeks, activity data from the actigraph were downloaded to a computer via the Actigraph Interface Unit. Five days of continuous monitoring were randomly sampled, which would account for approximately 80% reliability.[129] This 5-day period was included during the first two week period of the exercise program. The actigraphs were returned to the subjects and they were instructed to continue wearing them. At the end of four weeks, data from the actigraph were again downloaded. Continuous monitoring for 5 days was again randomly sampled from the second two week period. The actigraph data were again downloaded at the end of the sixth week and eighth week, with five days of continuous sampling for each of the 2 two week periods. There were regular telephone calls to remind patients to wear their actigraphs and to verify that the actigraphs were being worn properly. Table 1 lists the data collection time points and measures used.

Table 1. Data collection time points and measures to be used.

Time Point	Assessment/Data collection tool
Baseline	All subjects: Demographic info, PPT, MDASI, BFI, FACT-BMT, self-efficacy scale Actigraph subgroup: all of above + actigraph initialization
2 weeks	Actigraph subgroup: actigraph download
4 weeks	All subjects: PPT, MDASI, BFI, FACT-BMT, global perception of change Actigraph subgroup: all of above + actigraph download
6 weeks	Actigraph subgroup: actigraph download
8 weeks	All subjects: PPT, MDASI, BFI, FACT-BMT, global perception of change Actigraph subgroup: all of above + actigraph download

Adverse Events

If a participant experienced significant loss of muscle strength, proprioception, or balance to the point where he or she was unable to walk safely or perform self-care without the use of an assistive device (i.e., cane, walker, wheelchair, bedside commode, tub transfer bench or shower chair), then he or she was prescribed an assistive device. Prescription of an assistive device did not constitute grounds for removal from the study, nor did it constitute grounds for reporting an adverse event.

If a subject experienced changes in functional status (e.g., inability to care for self or increase in severity of peripheral neuropathy) that required individualized treatment beyond the parameters of this protocol, then the subject's physician was notified, and that subject was removed from the study. If a subject developed a significant complication from the BMT/PBSCT during the 8-week exercise period (e.g., severe infection that requires hospitalization), then he or she was removed from the study, and such complications were reported as external adverse events.

Falls are known to occur within this population due to muscular weakness and/or balance disorders. Generally these falls occur during self-care activities or during leisure and/or other meaningful activities of daily life, not typically during the performance of their exercise program. If a subject fell during daily activity or during exercise, then his or her physician was notified and the fall was documented as an adverse event. Severity of the fall, and other adverse events, was assessed on a case-to-case basis, with the subject removed from the study if the adverse event was severe.

APPENDIX B

Brief Fatigue Inventory

Brief Fatigue Inventory

Brief Fatigue Inventory

STUDY ID# ____________ HOSPITAL # ____________

Date: ____/____/____ Time: ____________

Name ____________ ____________ ____________
Last First Middle Initial

Throughout our lives, most of us have times when we feel very tired or fatigued.
Have you felt unusually tired or fatigued in the last week? Yes ☐ No ☐

1. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your fatigue right NOW.

0 1 2 3 4 5 6 7 8 9 10
No Fatigue — As bad as you can imagine

2. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your USUAL level of fatigue during past 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No Fatigue — As bad as you can imagine

3. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your WORST level of fatigue during past 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No Fatigue — As bad as you can imagine

4. Circle the one number that describes how, during the past 24 hours, fatigue has interfered with your:

A. General activity
0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely Interferes

B. Mood
0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely Interferes

C. Walking ability
0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely Interferes

D. Normal work (includes both work outside the home and daily chores)
0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely Interferes

E. Relations with other people
0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely Interferes

F. Enjoyment of life
0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely Interferes

APPENDIX C

M. D. Anderson Symptom Inventory – Bone Marrow Transplant

M.D. Anderson Symptom Inventory – BMT

Draft

Date: ☐☐ / ☐☐ / ☐☐
(month) (day) (year)

Subject Initials: ___________

Study Subject # ☐☐☐☐

Study Name
Protocol #
PI
Date

M. D. Anderson Symptom Inventory (MDASI - BMT)

Part I. How severe are your symptoms?

People with cancer frequently have symptoms that are caused by their disease or by their treatment. We ask you to rate how severe the following symptoms have been *in the last 24 hours*. Please fill in the circle below from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.

	Not Present 0	1	2	3	4	5	6	7	8	9	As Bad As You Can Imagine 10
1. Your pain at its WORST?	O	O	O	O	O	O	O	O	O	O	O
2. Your fatigue (tiredness) at its WORST?	O	O	O	O	O	O	O	O	O	O	O
3. Your nausea at its WORST?	O	O	O	O	O	O	O	O	O	O	O
4. Your disturbed sleep at its WORST?	O	O	O	O	O	O	O	O	O	O	O
5. Your feelings of being distressed (upset) at its WORST?	O	O	O	O	O	O	O	O	O	O	O
6. Your shortness of breath at its WORST?	O	O	O	O	O	O	O	O	O	O	O
7. Your problem with remembering things at its WORST?	O	O	O	O	O	O	O	O	O	O	O
8. Your problem with lack of appetite at its WORST?	O	O	O	O	O	O	O	O	O	O	O
9. Your feeling drowsy (sleepy) at its WORST?	O	O	O	O	O	O	O	O	O	O	O
10. Your having a dry mouth at its WORST?	O	O	O	O	O	O	O	O	O	O	O
11. Your feeling sad at its WORST?	O	O	O	O	O	O	O	O	O	O	O
12. Your vomiting at its WORST?	O	O	O	O	O	O	O	O	O	O	O
13. Your numbness or tingling at its WORST?	O	O	O	O	O	O	O	O	O	O	O

Draft

Date: ____________

Study Name
Protocol #
PI
Date

Subject Initials: ________

Study Subject # | | | | |

BMT	0 Not Present	1	2	3	4	5	6	7	8	9	10 As Bad As You Can Imagine
14. Your feeling physically sick at its WORST?	O	O	O	O	O	O	O	O	O	O	O
15. Your feeling physically weak at its WORST?	O	O	O	O	O	O	O	O	O	O	O
16. Your diarrhea (loose stools)at its WORST?	O	O	O	O	O	O	O	O	O	O	O
17. Your mouth sores at its WORST?	O	O	O	O	O	O	O	O	O	O	O
18. Your bleeding at its WORST?	O	O	O	O	O	O	O	O	O	O	O
19. Your problem with PAYING ATTENTION (Concentrating) at its WORST?	O	O	O	O	O	O	O	O	O	O	O

Part II. How have your symptoms interfered with your life?

Symptoms frequently interfere with how we feel and function. How much have your symptoms interfered with the following items *in the last 24 hours*:

	0 Did Not Interfere	1	2	3	4	5	6	7	8	9	10 Interefered Completely
19. General activity?	O	O	O	O	O	O	O	O	O	O	O
20. Mood?	O	O	O	O	O	O	O	O	O	O	O
21. Work (including work around the house)?	O	O	O	O	O	O	O	O	O	O	O
22. Relations with other people?	O	O	O	O	O	O	O	O	O	O	O
23. Walking?	O	O	O	O	O	O	O	O	O	O	O
24. Enjoyment of life?	O	O	O	O	O	O	O	O	O	O	O

APPENDIX D

Functional Assessment of Cancer Therapy – Bone Marrow Transplant (v.4)

(FACT – BMT)

FACT-BMT (Version 4)

Below is a list of statements that other people with your illness have said are important. By **circling one (1) number per line, please indicate how true each statement has been for you** __**during the past 7 days.**__

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please check this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

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

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	●	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

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

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
BMT1	I am concerned about keeping my job (include work at home)	0	1	2	3	4
BMT2	I feel distant from other people	0	1	2	3	4
BMT3	I worry that the transplant will not work	0	1	2	3	4
BMT4	The effects of treatment are worse than I had imagined	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
C7	I like the appearance of my body	0	1	2	3	4
BMT5	I am able to get around by myself	0	1	2	3	4
BMT6	I get tired easily	0	1	2	3	4
BL4	I am interested in sex	0	1	2	3	4
BMT7	I have concerns about my ability to have children	0	1	2	3	4
BMT8	I have confidence in my nurse(s)	0	1	2	3	4
BMT9	I regret having the bone marrow transplant	0	1	2	3	4
BMT 10	I can remember things	0	1	2	3	4
Br1	I am able to concentrate (e.g., reading)	0	1	2	3	4
BMT 11	I have frequent colds/infections	0	1	2	3	4
BMT 12	My eyesight is blurry	0	1	2	3	4
BMT 13	I am bothered by a change in the way food tastes	0	1	2	3	4
BMT 14	I have tremors	0	1	2	3	4
B1	I have been short of breath	0	1	2	3	4
BMT 15	I am bothered by skin problems (e.g., rash, itching)	0	1	2	3	4
BMT 16	I have trouble with my bowels	0	1	2	3	4
BMT 17	My illness is a personal hardship for my close family members	0	1	2	3	4
BMT 18	The cost of my treatment is a burden on me or my family	0	1	2	3	4

APPENDIX E

Self-Efficacy Scale

Self—efficacy scale

0% - 10 - 20 - 30 - 40 - 50 - 60 - 70 - 80 - 90 - 100% No confidence … Completely confident		Confidence Level
How confident are you that you can exercise when you are:	tired?	
	in a bad mood?	
	feel you don't have time?	
	on vacation?	
How confident are you that you could:	carry out your activity for the planned duration?	
	pace yourself to avoid over-exertion?	
	perform all the required movements?	
	follow directions from an instructor?	
	check how hard your activity is making you work?	
How confident are you that you could:	exercise two times per week regular for the next three months?	
	exercise three times per week for the next three months?	
	overcome obstacles that prevent you from participating regularly?	
	make up times you missed?	
	exercise regularly, no matter what?	

How often have you engaged in any physical activity over the last 4 weeks	
None	
Less than once a month	
About once a month	
About 2 or 3 times a month	
About 1 or 2 times a week	
3 times or more a week	

How often do you intend to engage in physical activity over the next 4 weeks?	
None	
Less than once a month	
About once a month	
About 2 or 3 times a month	
About 1 or 2 times a week	
3 times or more a week	

Listed below are obstacles other people have indicated get in the way of exercise. Which barriers affect/do not affect you; which have you been successful or unsuccessful in overcoming?	Does this affect you?		When this happens, do you usually overcome it?		If YES, how did you overcome it? (Use back if necessary)
	Y	N	Y	N	
Too tired					
Work too much					
Bad day at work					
Feel ill					
Don't feel like it					
Family commitments					
Have no time					
Too lazy/lack energy					
Health conditions					
Have bad back					
Lack self discipline					

APPENDIX F

Global Perception of Change

GLOBAL RATING SCALES

Please circle the appropriate response

Magnitude of Change

7 Improved a very great deal

6 Improved a great deal

5 Improved quite a bit

4 Improved moderately

3 Improved somewhat

2 Improved a little bit

1 Improved a tiny bit, almost the same

0 No change

-1 A tiny bit worse, almost the same

-2 A little bit worse

-3 Somewhat worse

-4 Moderately worse

-5 Quite a bit worse

-6 A very great deal worse

-7 A very great deal worse

Importance of Change

7 Change (better or worse) is very important

6

5

4

3

2

1

0 Change neither important nor unimportant

-1

-2

-3

-4

-5

-6

-7 Change (better or worse) not at all important

APPENDIX G

Patient Education Material

THE UNIVERSITY OF TEXAS
MD ANDERSON
CANCER CENTER
Making Cancer History™

Rehabilitation Services
BMT Discharge Class

Rehabilitation Services

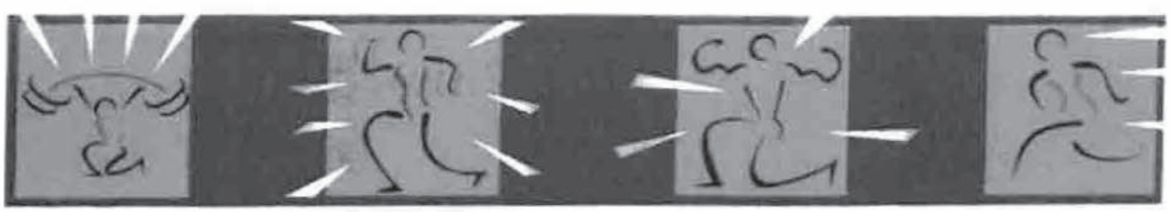
Some people may experience a decrease in strength and endurance during their treatment. Our rehabilitation department offers inpatient and outpatient physical, occupational, and speech therapies. Physical therapists assist patients in maintaining and regaining mobility, as well as providing guidance in an appropriate exercise program. Occupational therapists focus on training patients in self-care activities and safety awareness. Patients receiving these services may also participate in group activities such as exercise and cooking. Speech pathologists assist and treat speech, language, cognitive-linguistic, and swallowing functions. Referral to these services must be made by your physician based upon your needs; however, you can ask your physician to refer you if you feel you need our services. You can reach the **Department of Rehabilitation Services** at M. D. Anderson Cancer Center at **(713) 792-3192** and is located in the **Green Zone 1.3418** next to the GA elevators. Our outpatient department is open from 8:00 a.m. to 5:00 p.m.

Stay Active

It is imperative that you stay out of bed and move around as much as possible to keep your muscles and lungs in good shape. You will get a lot of exercise walking to and from all of your clinic appointments. Try not to use a wheelchair, if possible. Try to perform as much of your own self-care (bathing, dressing, etc.) as safely possible. Your doctor will typically not want you to utilize a public gym or swimming pool until you immune system has fully recovered. Check with him/her first before initiating those activities. For those who continue to require some dose of steroids, it may be very difficult for you to regain your strength. If you feel you are not able to get enough exercise during your day or are not sure what you should be doing, perhaps a consult to Rehab Services is in order. Some people may have tingling, burning, pain, or numbness in the feet and/or hands. Rehab services has treatments that may benefit you. Again, ask your doctor.

Caregivers

It is also imperative that YOU keep in good shape. Without you, our patients cannot make progress and succeed in their treatments. Make sure you take time to exercise, walk, and eat right. Exercising with your loved one benefits both of you and can help motivate both of you as well. However, checking with your doctor before starting an exercise program is a must.



STEROID MYOPATHY

Corticosteroids are used to treat graft-versus-host disease. This group of steroids can weaken the proximal muscle groups, that is, the muscles closest to the trunk, primarily in the hips and shoulders. "Steroid myopathy" refers to this weakening. If you are taking high doses of corticosteroids or have taken these steroids for a prolonged period of time, you may experience steroid myopathy. You may first notice difficulty in standing up from a low chair or from the toilet. You may also notice problems in reaching for objects above your head.

Steroids affect each individual differently. Some people will feel little to no weakness, while others may require special equipment to guarantee safety with walking, standing, or reaching for objects. Several factors determine the extent of the steroid myopathy and the length of time the myopathy lasts.

1) High dose versus low dose steroids
2) Length of time of prolonged steroid use without physical exercise intervention
3) Amount of time between initiation of steroids and exercise intervention
4) Current overall conditioning
5) Other medical or physical factors

The good news is that steroid myopathy is usually reversible once the steroids are discontinued; and exercise before and during steroid administration can help prevent weakness. You will be given an exercise program concentrating on shoulder and hip strengthening to perform every day. You will be able to do most of the exercises sitting or standing. With standing exercises, make sure you have a stable surface to hold onto while performing the exercises. Refer to the exercise packet for examples of activities you can perform to help avoid steroid myopathy.

We recommend you continue your normal activities within safe limits and fatigue levels. If you are overly fatigued or tired, limit your activities only to what must be accomplished. Perform exercises only while sitting or lying down. Use assistive devices, such as a cane or walker, when walking, standing, or transferring. Make sure someone is close by to help you if you need something. Take rest breaks frequently.

Blood Counts and Exercise

Use caution when exercising with very low blood counts. Hemoglobin below 8.0 can result in abnormal shortness in breath, dizziness or light-headedness, or increased fatigue. Platelets below 10,000 increase the risk of bleeding. Exercising into maximum ranges where you are straining or using maximal effort to perform the exercise can result in bleeding in muscle tissues and joints. White blood cell counts that are less than 1.0 place you at a greater risk for infection. It is imperative that you maintain strict infection control methods: Wear mask and gloves when exercising in public and practice good hand washing.

Based on the information given above, we recommend exercising in ranges of moderate effort, where you feel challenged but are able to perform 2-3 sets of 10 repetitions without difficulty. On days when your counts are low, you may exercise if you feel you can but exercise in minimal ranges of effort. In your exercise packets, you will have a set of exercises for when you are feeling well and your counts are above the limits and another set of exercises for when your counts are low or you are not feeling as well. Adhere to these guidelines for your safety.

Cases when exercise should be avoided are if you are actively bleeding, are extremely short of breath, or your fatigue level is greater than 9 on a scale of 0 to 10. (See exercise tolerance for explanation of the fatigue scale.)

Exercise Tolerance

Vital signs and fatigue levels have to be monitored in order for you to exercise safely. Vital signs that need monitoring are listed below with methods to monitor them.

Heart rate—the number of heart beats per minute

Find your pulse on your wrist with your index and middle finger.

Count the number of beats for 30 seconds. Multiply the number by 2.

OR count the number of beats for 15 seconds and multiply the number by 4.

This number should not exceed your maximal target heart rate (220 – your age = maximal target heart rate) Normal ranges at rest should be 60-80 beats per minute. Due to medications you may be taking, your heart rate may be much higher. Ask your doctor about acceptable heart rate limits when you exercise.

Respiratory rate—the number of breaths you take per minute

Count the number of breaths you take in a minute.

Normal ranges at rest should be 12-20 breaths per minute. When performing aerobic exercises, your respiratory rate will become much higher. This is fine as long as you are not gasping for air, feel short of breath, or have difficulty slowing your breathing rate. It is best to start aerobic exercise at lower rates to determine how your body is going to react.

Blood pressure—the pressure exerted on the blood vessels by blood flow

To manually take your blood pressure, someone needs to assist you. Have them follow these instructions.

1) Apply a blood pressure cuff to the left arm just above the elbow.
2) Place the stethoscope on the inside of the elbow.
3) With the arm raised to heart level and supported so the person can relax, pump the cuff up until the pressure reaches approximately 180.
4) Slowly release the pressure and listen for a heart beat when watching the pressure gauge. The first heartbeat will be the systolic (the top number) of the blood pressure.
5) Continue to release the pressure until you can no longer hear the heart beat. The pressure at which the heartbeat disappears is the diastolic pressure (the bottom number).

To electronically take your blood pressure, apply the cuff and follow the directions on the machine.

Normal range is 120/80. Your blood pressure may fluctuate greatly depending on the medications you are taking. Be aware of what your blood pressure is normally in the clinic and watch for symptoms that may indicate low or high blood pressure. Low blood pressure can cause dizziness, light-headedness, and the feeling of being faint. These symptoms often occur when changing positions quickly such as sitting up after lying down or standing up from sitting. Extremely low pressure can cause fainting spells and subsequent injury. High blood pressure can cause headaches, and tunnel vision. If you are experiencing these symptoms, do not exercise without notifying your doctor or physical therapist. They will tell you if you are safe to proceed with exercise.

Rate of perceived exertion—how hard you feel you have been working

Assess how you feel physically. Use the chart below to rate your perceived exertion.

0--------Nothing at all
0.5-----Very, very weak
1--------Very weak
2--------Weak
3--------Moderate
4--------Somewhat strong
5--------Strong
6
7--------Very strong
8
9
10------Very, very strong (Maximal)

Fatigue level—a rating on a scale from 0 – 10

"0" means you have no fatigue.

"10" means you are so fatigued you cannot force yourself out of bed.

This number may fluctuate throughout the day. Even with fatigue levels of 7-8 out of 10, you should try to perform some exercise. However, you should not exercise to the point of 10/10 fatigue levels because your body could take several days to recover.

All of these factors contribute to your overall sense of well-being. Other factors may include body aches and pain, nausea, vomiting, diarrhea, general "not feeling well," headache, etc. If you have any questions on whether or not to exercise, consult your doctor.