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Pre-transplant Exercise and Hematopoietic Cell Transplant Survival: a secondary analysis of Blood and Marrow Transplant Clinical Trials Network (BMT CTN 0902)

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Abstract

Blood and Marrow Transplant Clinical Trials Network (BMT CTN) Protocol 0902 evaluated whether exercise and stress management training prior to hematopoietic cell transplantation (HCT) improved physical and mental functioning after HCT. Neither overall survival nor other patient-reported transplant outcomes were improved by the training intervention. In some animal studies of HCT, moderate intensity exercise for 8 weeks before HCT has been associated with positive effects on hematopoietic progenitors resulting in improved donor engraftment and improved survival. Accordingly, we performed a secondary analysis of data from BMT CTN 0902 to determine whether exercise engagement prior to HCT was associated with engraftment and survival. There were no significant associations between self-reported pre-HCT exercise levels and engraftment or survival. There was also no effect of pre-transplant exercise on either neutrophil or platelet engraftment. These findings do not support the observations in animal models but are limited by several shortcomings that do not refute the hypothesis that exercise before HCT may be beneficial.

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Keywords

Hematopoietic; transplant; allogeneic; exercise

Introduction

Engagement in moderate intensity exercise several times a week has been associated with multiple health benefits. Several studies suggest some of these benefits may be due to effects on differentiated hematopoietic lineage cells (1-3) through enhancement of immune function and erythrocyte content. Exercise training in mice has been associated with an increase in the quantity of hematopoietic stem cells (HSC) in the vascular niche, but not in the endosteal niche, of the bone marrow (4). In one study in mice undergoing HCT, exercise training of the recipient before HCT substantially increased recipient survival (5). Exercise training occurred for one hour daily, three days a week for 8 weeks using a motorized treadmill. Control mice were placed on the non-moving treadmill. In that experiment, the mice were inadvertently subjected to stress (movement of the cages just before HCT) and the investigators conjectured that stress increased the mortality in the non-exercised cohort while exercising mice were not affected. The increase in survival with exercise was associated with a decrease in proinflammatory cytokine levels, inhibition of marrow cell loss by apoptosis, and higher percentages of circulating donor-derived leukocytes early after transplant (5). In humans, exercise training initiated after transplant has shown benefits in some studies but not in others (6,7), with relatively few studies evaluating pre-transplant exercise (8). A reduction in inflammatory cytokines produced by exercise before the cytotoxic conditioning regimen has been suggested as an explanation for a decrease in the inflammatory response after HCT and promotion of survival (5).

In the BMT CTN 0902 trial (9), the effect of exercise training alone, stress management training alone, and both together during the transplant period were compared with neither to determine effects on physical and mental status at 100 days. There were no beneficial effects of the interventions noted in physical or mental status, a variety of patient-reported outcomes, or in overall survival at 100 or 180 days or at one year. Since the animal studies suggested that exercise before HCT might offer beneficial effects not seen with exercise after HCT, in this secondary analysis, we tested whether self-reported pre-transplant exercise levels were associated with engraftment and survival. Since one murine study also suggested exercise might mitigate the deleterious effect of stress on transplant survival (5), we also examined the interaction of self-reported stress and exercise before HCT using data from the BMT CTN 0902 study.

Methods

Patients

The parent trial, BMT CTN 0902, was a 4 arm randomized study to test the effects of exercise training, stress management training, both, or neither on various post-transplant outcomes, including patient-reported outcomes and survival (9) (Clinical-Trials.gov identifier: NCT01278927; protocol available at www.bmtctn.net). Patients 18 years of age or

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older with the ability to exercise at low to moderate intensity and who were undergoing autologous or allogeneic HCT were eligible. A total of 711 patients at 21 centers were enrolled. This secondary analysis focuses on the subset of 310 allogeneic HCT recipients. The characteristics of the patients are described in Table 1. The baseline instruments were collected up to 6 weeks prior to admission for HCT. After enrollment and collection of self-reported measures, participants were randomized and received their assigned training. Self-reported data were collected longitudinally after transplant, and clinical outcomes were abstracted from medical records. The protocol was IRB-approved by all participating institutions, and all subjects provided written informed consent.

Measures

Self-reported exercise was assessed before HCT using the Leisure Score Index (LSI) of the Godin Leisure-Time Exercise Questionnaire (10). The LSI captures exercise in the past week, as mild, moderate, or strenuous based on exertion. The number of minutes was recorded. A weekly leisure activity score was calculated by weighting and adding the amount of exercise performed with the three intensities, according to scoring directions. Standard cutoffs were used (<14, 14-23, >=24) with higher scores indicating more exercise. The Physical Functioning (PF) subscale of the Short Form-36 Health Survey (11) version 2.0 was also used to explore possible confounding in that patients with better physical functioning might be exercising more. For the PF subscale, a score of 85 (possible range 0 – 100) was used as the cutoff with higher scores indicating better functioning, based on an optimal cutpoint analysis. In view of the possible influence of stress noted in the animal model (5), self-reported stress before HCT was also assessed, using the Cancer and Treatment Distress (CTXD), a 27-item measure of distress (12,13). Cutoffs of <=1.1, >1.1 were used with higher scores reflecting greater distress. Time to engraftment was defined as the first day to recovery of neutrophils to greater than 500/ml for 3 consecutive days. Intensity of the conditioning regimen was dichotomized as myeloablative (MA) or reduced intensity conditioning (RIC).

Analysis

The effects of self-reported pre-HCT exercise and stress were tested for association with 180-day overall survival using a Cox proportional hazards regression model. Adjustment for the possible confounding effect that patients with better physical functioning might be exercising more was performed by inclusion of PF into another Cox model. To evaluate impact of these variables on 180-day overall survival, we enforced censoring on all surviving patients at day 180. The second Cox model, assessing LSI, CTXD, and PF as main effects, adjusted for patient and treatment related variables, including age, race (white or not), marital status, education level, employment status, household income level, Karnofsky performance score, alcohol use (yes/no), tobacco use (yes/no), body mass index at baseline, hematopoietic cell transplantation-specific comorbidity index (HCT-CI), disease risk index, cytomegalovirus (CMV) status, time from diagnosis to transplant, prior transplant (yes/no), conditioning regimen (myeloablative or not), donor/recipient matching, graft type (bone marrow, peripheral blood, or cord blood), anti-thymocyte globulin (ATG)/Campath use, and GVHD prophylaxis. Stepwise variable selection at a 0.05 significance level was used to choose the patient and transplant related variables to include in the final linear and

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generalized linear models. In addition, the effects of exercise were tested on neutrophil and platelet engraftment using Cox models and adjusted for the effect of conditioning regimen intensity (ablative versus reduced intensity). No covariate was found to violate the proportionality assumption in any of the Cox models. All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC).

Results

Table 1 shows patient characteristics. The median age was 54 years and 44% had myeloablative conditioning. Exercise engagement was low pre-HCT, with a median LSI score of 13 (interquartile range, [IQR] 5-31). The median physical component score (PCS) from the SF-36 was 44 (IQR 36-51), more than half a standard deviation below the general population average of 50.

There was no association of exercise (LSI score <14) before HCT with survival at 180 days (HR = 1.70, 95% CI 0.96-2.99) compared to those with the highest level of exercise (LSI score >24); an overall test of the effect of exercise grouping was not significant (p=0.11) (Table 2). When PF was added to the model the effect of pre-transplant exercise remained insignificant (HR = 1.44, 95% CI 0.81-2.56, p=0.21), while PF was highly significant (HR 2.51, 95% CI 1.29-4.89, p=0.0068) (Table 3).

To determine if demographic or other treatment related factors could be confounders, we ran a stepwise variable selection of these variables to identify potential confounders for inclusion in the final model (Table 4). Household income level and HCT-CI were selected, but did not significantly impact the estimates of the main effects. An interaction of LSI and PF was tested and not found to be significant (p = 0.64 from a 2 df test). An interaction of LSI and conditioning regimen (MAC vs. RIC) was tested in a separate bivariate model and not found to be significant (p = 0.67 from a 2 df test). DRI and conditioning intensity did not significantly affect day 180 survival nor did they change the estimated effects of LSI, CTXD, or PF appreciably when forced into the model. A post-hoc power analysis estimated that we had 80% power to detect a 12.8% difference in day 180 survival for patients with LSI >= 14 and those with LSI < 14. Equivalently, we had 80% power to detect a hazard ratio of 1.99 for patients with LSI < 14 compared to those with LSI >= 14.

We also dichotomized exercise according to whether 150 minutes of exercise was performed per week. Evaluated in a Cox model that adjusted for PF, stress, and HCT-CI, this classification of exercise also had no effect on survival (HR = 1.19, 95% CI 0.63-2.25, p = 0.60). Exercise, as measured by LSI grouping, was also not associated with the rapidity of either neutrophil or platelet engraftment (HR = 1.00, p = 0.85 and HR = 1.00, p = 0.34 for neutrophil and platelet engraftment, respectively), irrespective of conditioning regimen intensity (data not shown).

Discussion

In an experimental mouse model of allogeneic HCT evaluating the effects of pre-HCT exercise on survival, the group that exercised one hour per day, three times per week for 8 weeks had higher survival rates compared to sedentary mice, and exercise seemed to protect

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mice subjected to stress prior to HCT (1,5). Additionally, pre-HCT exercise had important effects on both hematopoietic and immune cells consistent with an exercise effect on inhibition of marrow cell apoptosis, effects on the microenvironment, increases in progenitor quantity in the vascular niche, and modulation of proinflammatory cytokines associated with regulation of hematopoiesis (1,5,14-16) that result in improved donor engraftment and survival. Such observations in animal HCT models prompted this inquiry. Unfortunately, the data in this clinical trial do not substantiate the animal model findings or the limited clinical studies.

Several observations in humans undergoing HCT have also provided support to a benefit of exercise on HCT survival (7,17,18) but involved mostly exercise after transplant, not before. One small randomized trial that included exercise training both before and after transplant also suggested a benefit although it was not designed to test this effect and did not control for potentially confounding prognostic factors (19).

We previously reported an association between the physical component score and mortality in allogeneic but not autologous HCT patients enrolled in this BMTCTN trial (20). Although one would expect some overlap between physical function and exercise, at each level of physical function there can be considerable variability as to the level of exercise. This analysis would suggest that function exerts a more powerful influence on survival than engagement in exercise.

There are several limitations to this analysis. First, the trial was not focused on pre-HCT exercise and the patients' self-reported exercise information was reliant on recall at a time when the patients were subjected to the stresses associated with preparation for HCT. Second, our group had LSI and PF scores that are significantly lower than norms with few reaching the duration and intensity tested in the murine study. Participants had not been trained or encouraged to vigorously exercise prior to the baseline assessment, limiting the range of exercise extremes, and, unlike the animal experiment, the subjects were not forced to increase their usual exercise. The exercise in the animal experiments was of longer duration than the self-reported duration reported at baseline in this analysis. Third, the exercise instrument measured exercise in the week prior to transplant. This is a time when the recipients are undergoing multiple medical tests and appointments and taking care of the multiple tasks needed for preparation for the transplant procedure; thus, their usual exercise patterns may have been disrupted and may not be accurately reflected in the activities during the interval of the LSI assessments. Fourth, the activity assessment was by self-report using response categories that may not be natural for people. Perhaps respondents tend to conflate their recalled experience of exercise with their perception of their physical functioning. A more objective assessment of exercise (e.g. activity monitor) would provide a more accurate exercise measurement than the Godin LSI instrument.

Although this secondary analysis does not support an association between pre-HCT exercise training and successful HCT, in view of the profound biological effects of pre-HCT exercise on hematopoietic and lymphopoietic precursors, this is a topic deserving of further inquiry using an experimental design with regimented approach to exercise before HCT. Patients

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planning to undergo HCT might be willing to undertake an exercise regimen if they felt it might help them better endure the rigors of transplantation.

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Table 1

Characteristics of allogeneic HCT recipients in the study cohort.

Variable	
Number of enrolled patients	310
Number of centers	19
Age at transplant, years, median(range)	54 (20-75)
Recipient sex, n (%)	
Male	173 (56)
Female	137 (44)
Karnofsky score, %, n (%)	
≥ 90	190 (61)
70 - 80	113 (36)
50 - 60	5 (2)
Missing/Not done	2 (<1)
Disease, n (%)	
AML/ALL	163 (53)
CML	12 (4)
MDS/MPN	44 (14)
MM/PCD	14 (5)
Lymphoma	57 (18)
CLL/SLL	20 (6)
Hematopoietic cell transplantation-specific comorbidity index (HCT-CI), n (%)	
0	108 (35)
1-2	93 (30)
3+	106 (34)
Missing	3 (<1)
Disease risk index[a] (DRI), n (%)	
Low	54 (17)
Intermediate	144 (46)
High	52 (17)
Very high	11 (4)
Missing	49 (16)
EBMT score, n (%)	
1	58 (19)
3	73 (24)
4	137 (44)
6	42 (14)
Prior transplant, n (%)	
No	267 (86)
Yes	43 (14)
Conditioning intensity, n (%)	
Myeloablative (MAC)	135 (44)

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Variable	
Reduced intensity (RIC)	175 (56)
Graft type, n (%)	
Bone marrow	39 (13)
Peripheral blood	246 (79)
Double cord blood	25 (8)
Baseline SF36 Physical Component Score	
Median	44
IQR	36-51
Range	13-65
Baseline SF36 Physical Functioning subscale	
Median	75
IQR	55-90
Range	5-100
CTXD at baseline	
Median	1.1
IQR	0.8-1.6
Range	0.0-3.0
LSI at baseline	
Median	13.0
IQR	5-32
Range	0-350
Missing	19
Exercise Intervention, n (%)	
No	150 (48.4)
Yes	160 (51.6)
Stress Intervention, n (%)	
No	157 (50.6)
Yes	153 (49.4)
Median follow-up of survivors (range),months	23 (6-35)

Abbreviations: AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; CML, chronic myeloid leukemia; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm; MM, multiple myeloma; PCD, plasma cell dyscrasia; CLL, chronic lymphocytic leukemia; SLL, small lymphocytic lymphoma; HCT-CI, hematopoietic cell transplantation comorbidity index; EBMT, European Blood and Marrow Transplant Group; SF36, Short Form 36; IQR, interquartile range; CTXD, Cancer and Treatment Distress; LSI, leisure score index

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Table 2
Mortality predicted by exercise (LSI) and stress (CTXD)

Effect	N	Hazard Ratio of Death	95% CI	p-value
LSI at baseline:				0.11 (2 df)
>= 24	99	1.00	-	
14-23	46	0.98	(0.42, 2.27)	
< 14	146	1.70	(0.96, 2.99)	
CTXD at baseline:				
<= 1.1	158	1.00	-	
> 1.1	152	1.36	(0.84, 2.22)	0.21

Abbreviations: LSI, leisure score index; CTXD, Cancer and Treatment Distress

- For factors with more than two categories, p-values are shown for individual categories only if the overall 2 degree of freedom test was significant.

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Table 3

Model of Mortality predicted by exercise (LSI), stress (CTXD) and physical functioning (the PF subscale of SF-36)

Effect	N	Hazard Ratio of Death	95% CI	p-value
LSI at baseline:				0.24 (2 df)
>= 24	99	1.00	-	
14-23	46	0.84	(0.36, 1.96)	
< 14	146	1.44	(0.81, 2.56)	
CTXD at baseline:				
<= 1.1	158	1.00	-	
> 1.1	152	1.18	(0.72, 1.93)	0.52
PF at baseline:				
>= 85	105	1.00	-	
< 85	205	2.51	(1.29, 4.89)	0.0068

Abbreviations: LSI, leisure score index; CTXD, Cancer and Treatment Distress; PF, physical function

- For factors with more than two categories, p-values are shown for individual categories only if the overall 2 degree of freedom test was significant.

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Table 4

Final model of Mortality predicted by exercise (LSI), stress (CTXD) and physical functioning (the PF subscale of SF-36) when other potential confounders were considered

	Effect	N	Hazard Ratio of Death	95% CI	p-value
Main Effects	**LSI at baseline:**				0.078 (2 df)
	>= 24	99	1.00	-	
	14-23	46	1.09	(0.45, 2.67)	
	< 14	146	1.92	(1.01, 3.63)	
	CTXD at baseline:				
	<= 1.1	158	1.00	-	
	> 1.1	152	0.95	(0.55, 1.64)	0.85
	PF at baseline:				
	>= 85	105	1.00	-	
	< 85	205	2.24	(1.10, 4.55)	0.026
Other Covariates	**Income level:**				0.011 (2 df)
	Over $75,000	132	1.00	-	
	$25,000 – 75,000	116	1.88	(1.07, 3.30)	0.029
	$25,000 or less	42	0.52	(0.17, 1.55)	0.24
	Comorbidity score:				
	0-2	201	1.00	-	
	>2	106	1.78	(1.06, 2.99)	0.029

Abbreviations: LSI, leisure score index; CTXD, Cancer and Treatment Distress; PF, physical function

- For factors with more than two categories, p-values are shown for individual categories only if the overall 2 degree of freedom test was significant.