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Pretransplantation Exercise and Hematopoietic Cell Transplantation Survival: A Secondary Analysis of Blood and Marrow Transplant Clinical Trials Network (BMT CTN 0902)

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Blood and Marrow Transplant Clinical Trials Network (BMT CTN) protocol 0902 evaluated whether exercise and stress management training before hematopoietic cell transplantation (HCT) improved physical and mental functioning after HCT. Neither overall survival nor other patient-reported transplantation 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 before HCT was associated with engraftment and survival. We found no significant associations between self-reported pre-HCT exercise levels and engraftment or survival. There was also no effect of pretransplantation 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.

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 in the vascular niche but not in the endosteal niche of the bone marrow [4]. In 1 study in mice undergoing hematopoietic cell transplantation (HCT), exercise training of the recipient before HCT substantially increased recipient survival [5]. Exercise training occurred for 1 hour daily, 3 days each week for 8 weeks using a motorized treadmill. Control mice were placed on the nonmoving 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 nonexercised cohort whereas the 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 transplantation [5]. In humans, exercise training initiated after transplantation has shown benefits in some studies but not in others [6,7], with relatively few studies evaluating pretransplantation 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 Blood and Marrow Transplant Clinical Trials Network (BMT CTN) 0902 trial [9], the effect of exercise training alone,

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stress management training alone, and both together during the transplantation 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 1 year. As 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 pretransplantation exercise levels were associated with engraftment and survival. Because 1 murine study also suggested exercise might mitigate the deleterious effect of stress on transplantation 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-transplantation 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 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 before 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 transplantation and clinical outcomes were abstracted from medical records. The protocol was approved by the institutional review boards of 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 3 intensities, according to scoring directions. Standard cutoffs were used (<14, 14 to 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 to 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 and >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 or reduced-intensity conditioning.

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 status, time from diagnosis to transplantation, prior transplantation (yes/no), conditioning regimen (myeloablative or not), donor/recipient matching, graft type (bone marrow, peripheral blood, or cord blood), antithymocyte globulin/Campath use (Genzyme Corp., Cambridge, MA), and graft-versus-host disease prophylaxis. Stepwise variable selection at a .05 significance level was used to choose the patient- and

Table 1
Characteristics of Allogeneic HCT Recipients in the Study Cohort

Variable	Value
No. of enrolled patients	310
No. of centers	19
Age at transplantation, median (range), yr	54 (20-75)
Recipient sex	
Male	173 (56)
Female	137 (44)
Karnofsky score, %	
≥90	190 (61)
70-80	113 (36)
50-60	5 (2)
Missing/not done	2 (<1)
Disease	
AML/ALL	163 (53)
CML	12 (4)
MDS/MPN	44 (14)
MM/PCD	14 (5)
Lymphoma	57 (18)
CLL/SLL	20 (6)
HCT-CI	
0	108 (35)
1-2	93 (30)
3+	106 (34)
Missing	3 (<1)
Disease risk index	
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 transplantation	
No	267 (86)
Yes	43 (14)
Conditioning intensity	
Myeloablative	135 (44)
Reduced intensity	175 (56)
Graft type,	
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 PF subscale	
Median	75
IQR	55-90
Range	5-100
CTXD at baseline	
Median	1.1
IQR	.8-1.6
Range	.0-3.0
LSI at baseline	
Median	13.0
IQR	5-32
Range	0-350
Missing	19
Exercise intervention	
No	150 (48.4)
Yes	160 (51.6)
Stress intervention	
No	157 (50.6)
Yes	153 (49.4)
Median follow-up of survivors (range), mo	23 (6-35)

Data presented are n (%) unless otherwise indicated.
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; EBMT, European Blood and Marrow Transplant Group; SF36, Short Form 36.