Physical exercise in patients with hematological malignancies

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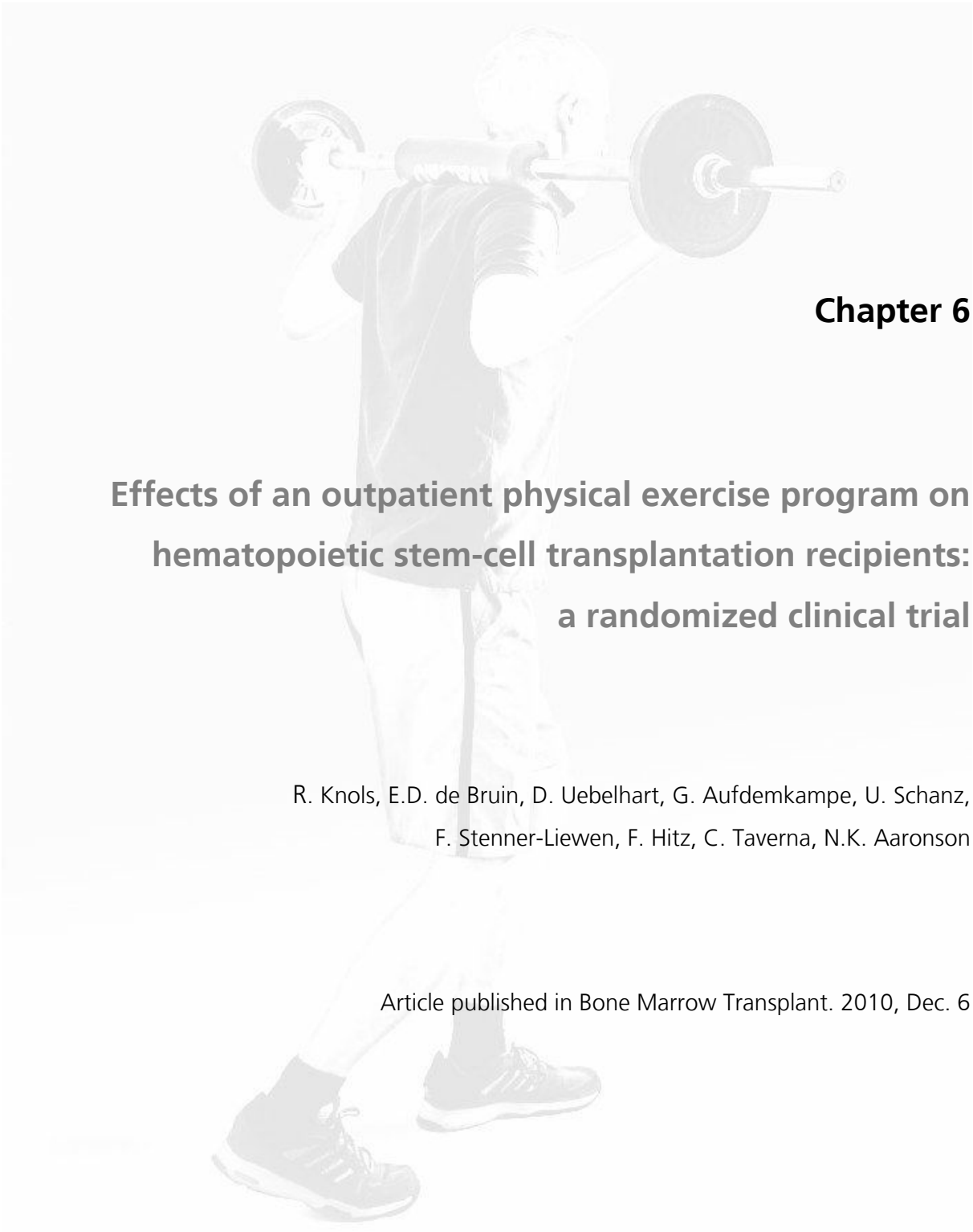

Chapter 6

Effects of an outpatient physical exercise program on hematopoietic stem-cell transplantation recipients: a randomized clinical trial

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Summary

Purpose

Patients who undergo hematopoietic stem cell transplantation (HSCT) often experience physical and psychological problems, even long after treatment has been completed. This study was performed to evaluate the effects of a 12-week outpatient physical exercise program, incorporating aerobic and strength exercises, as compared to a usual care control condition on patients' physical performance and psychosocial well-being.

Methods: Patients who had completed HSCT up to 6 months earlier were randomly assigned to a supervised physical exercise program (n = 64) or a usual care control group
(n = 67). Primary outcomes were quantified physical performance and self-reported physical functioning. Secondary outcomes were body composition measurement, quantified walking activity and patient-reported outcomes (physical activity, fatigue and health-related quality of life). Assessments were at baseline, immediately after program completion and at 3-month follow-up.

Results: Significant intervention effects were observed at both post-treatment and follow-up on physical performance measures. No other outcomes yielded statistically significant group differences.

Conclusion: Physical exercise should be considered in the management of HSCT recipients to improve physical performance after discharge from hospital. Further research is needed to determine how the program can be enhanced so that improved physical performance also translates into improved physical and psychosocial functioning in daily life.

Background

The number of hematopoietic stem cell transplantation (HSCT) survivors is increasing rapidly. Annually, more than 45,000 patients undergo HSCT worldwide [1]. HSCT is associated with considerable physical and psychological distress [2], which may have a significant impact on health-related quality of life (HRQOL), even years after completion of treatment [3]. HRQOL is a multidimensional construct, typically including physical, emotional and psychological health issues [4].

Physical exercise (PE) has been demonstrated to improve physical and psychological health outcomes in breast [5], prostate [6], and head and neck cancer patients [7], and may be particularly helpful in maintaining or improving physical functioning [5,7]. In HSCT patients, PE has been proposed as a means of helping individuals recover from the de-conditioning and the associated loss of functional capacity and debilitating fatigue that can occur with prolonged lack of physical activity after the transplantation phase [8,9]. However, heterogenous effects of PE on psychological well-being (e.g., HRQOL) have been reported across studies [2].

After discharge from hospital, positive effects of outpatient PE programs have been reported for both physical and psychological health outcomes [2,10]. Yet, few randomized clinical trials (RCT) have investigated the effectiveness and the therapeutic sustainability of an outpatient PE intervention on self-reported HRQOL [2].

Most outpatient physical exercise (PE) interventions after HSCT have involved isolated aerobic exercise programs or strength training [2]. To add strength resistance training to the aerobic intervention may be important for increasing muscle strength and bone and muscle mass [2]. To date, few studies have combined both aerobic and strength exercise components in a single program [2].

In general, the quality of previous studies has been less than optimal [2,11]. In particular, most have been single-group studies, or controlled clinical trials or RCT's without appropriate randomization methods. Relevant methodological safeguards such as concealment of treatment allocation, use of intention-to-treat analyses and blinding have not been used consistently [2,12]. Several studies reported data from trials with small samples and a high percentage of loss to follow-up [2]. This underscores the need for larger RCTs of physical exercise interventions in HSCT recipients.

A challenge for researchers is that many HSCT patients are quite ill and unable to follow the standard guidelines for physical exercise as recommended by the American College of Sports medicine (ACSM) [11,13]. Thus, we designed a program in which participants performed a graded exercised endurance and strength program [13]. We hypothesized that a moderate supervised outpatient physical exercise program for HSCT recipients would be superior to usual care in enhancing physical performance, body composition, quantified walking activity, self-

reported physical activity, fatigue and self-reported HRQOL as assessed both immediately following the training program and at 3-month follow-up.

Methods

Study sample

The study sample included both male and female patients who were older than 18 years of age, who had at least a basic fluency in the German language, and were recruited from three weeks up to six months after autologous or allogeneic HSCT. All patients were recruited from the University Hospital Zurich and the Cantonal Hospital St. Gallen. Patients were excluded from the study in the case of graft versus host disease (except for grade I not requiring treatment), painful joints, instable osteolyses, chronic pain, lesions of the central or peripheral nervous system, uncontrolled cardiovascular disease, thyroid disease or diabetes. The ethical committees of the Cantons Zurich and St. Gallen approved the study. All patients provided written informed consent. The study was registered at clinicaltrials.gov (number NCT00402753).

Design and procedures

The study was a prospective, two group randomized clinical trial (RCT) investigating the effect of an ambulatory PE program compared to an usual care control group (UCG), with assessments at baseline, after completion of the exercise program or an equivalent time point for the usual care condition, and at 3-month follow-up. All patients underwent physical performance tests and body composition measurements, and completed questionnaires at the same time of day. The patients wore an accelerometer during 7 days to assess daily walking activity.

Random assignment and blinding

A minimization procedure [14] was used to achieve an optimal balance between groups for the factors age, sex and type of transplantation (autologous versus allogeneic HSCT) (Figure 1). The patients were randomly allocated to PE or to the usual care group (UCG) after the baseline measurements were performed. The results of the randomization were stored in opaque envelopes. The allocation sequence and contents of the envelopes were concealed from the study personnel. Independent assessors who were blinded to group assignment carried out the assessments. The trainers of the PE intervention could not, by definition, be blinded.

Physical exercise intervention and control group

The PE group received a 12-week, supervised physical exercise program, incorporating both endurance and resistive strength exercises. The program was performed twice weekly in a physiotherapy practice or fitness centre near the patient's home. A physiotherapist or a physical

trainer was present during the PE program to provide patients with further instructions and to guarantee their safety. Ergometer-cycling was used as cardiovascular training. All patients started with a 10-minute warming-up on an ergometer-cycle or a walking tread-mill. The exercise was built up to maintain the aerobic performance for at least 20 minutes, at a pre-defined individual heart rate (from 50-60%, increasing up to 70-80% of the estimated maximum heart rate) [2]. The maximum heart rate was determined by subtracting the patient's age from 220 [13].

Cardiovascular training was combined with progressive resistance training to address cancer-related decrease in muscle strength [15]. This training was done using dumbbells in order to also address physical coordination. The standard strength program included squats, step-ups and downs, barbell rotations, and upright rowing. The program could be extended with chest press, triceps extension, biceps curl, modified curl ups, and calf raises. Patients in the usual care group (UCG) received usual care, which did not involve any structured or supervised exercise, or any encouragement to do physical exercise.

Study measures

Sociodemographic and clinical data

Age, sex, education, marital status, and leisure time activity [16] were obtained via personal interview. Clinical variables, including diagnosis, stem cell donor type, and time interval between HSCT and study assessments were obtained from the patients' medical records (table1). Adherence to the exercise program was assessed using an exercise diary kept by the patient. Patients were also requested to report non-protocol exercise and any adverse events associated with the exercise program.

Primary outcome measures

A set of physical performance measures (knee extension and grip strength, walking speed, functional exercise capacity, table 2, and the physical function subscale of the EORTC QLQ-c30, table 3, were used as primary outcome measures).

Knee extension strength (maximum voluntary peak force in Nm) was assessed with a hand-held dynamometer (HHD, CompuFet, Hoggan Health Industries Inc, West Jordan, UT, USA) that has previously been shown to be reliable in patients with hematological malignancies (table 2) [17].

Grip strength (Kg) was assessed with a Jamar hydraulic dynamometer (Lafayette Instrument type J00105, Lafayette, IN, USA) which has good intra-tester reliability and concurrent validity table 2) [18].

Walking speed was measured with a 50 foot (15.24 meter) walk test. The inter-tester agreement for this test is good (table 2) [19].

Functional exercise capacity was assessed with the six minute walking test (6-MWT in meters), a widely used, reliable, sub-maximal exercise test that assesses the physiologic and functional status of patients (table 2) [19].

Self-reported physical function was assessed with the German language version of the EORTC QLQ-C30 [4]. The QLQ-C30 is used widely in cancer clinical trials, and has been demonstrated to be both valid and reliable (table 3) [4].

Secondary outcomes

Body composition

Body composition, including weight, fat mass and fat free mass (table 4) was measured with dual x-ray absorbtiometry (DXA) using the Hologic QDR (Discovery 4500A, Montreux Switzerland) [20].

Quantified walking activity

Walking activity, including daily average steps and peak activity, was quantified with the Step Activity Monitor 3 (SAM3, Cymatech Corporation, Seattle, WA, USA). Patients wore the SAM3 for 7 consecutive days, yielding a reliable and representative measure of movements on a day-to-day basis [21]. Due to the properties of the SAM3, none of the patients received feedback about the step watch measurements at any time during the study [22]. The SAM3 was programmed to start the day after assessments, were made in the patient's environment. The quantified walking assessments were performed before and after the physical exercise program (table 5).

Physical activity, fatigue and HRQOL (Patient-reported outcomes)

Self-reported physical activity (total met-minutes / week) was assessed with the International Physical Activity Questionnaire (IPAQ) short-form, telephone-version (table 5). The IPAQ has adequate test re-test properties for monitoring group level physical activity in diverse settings [23].

Fatigue was assessed with the German language version of the fatigue subscale of the Functional Assessment of Cancer Therapy /Anaemia Scale (FACT / An), which has excellent reliability (table 5) [24].

HRQOL (tables 6 and 7) was assessed with the German language version of the EORTC QLQ-C30 (except for physical function, which was a primary outcome, table 3). The QLQ-C30 is used widely in cancer clinical trials, and has been demonstrated to be both valid and reliable [4].

Statistical analyses

The a-priori power analyses for a comparison between the randomized groups estimated a minimal requisite sample size of 64 patients per group in order to detect a moderate effect size (d=0.50) with a power of 0.80 and a two tailed alpha of 0.05. Baseline comparisons were performed using an independent Student's t-test, the $\chi 2$ test [25]. All data were checked for allowable ranges, missing data and extreme values. In the final analyses, we did not perform any imputations. Multilevel linear models analyses (MLMA) [25], were used to compare differences between the PE group and the usual care group over time (baseline to follow-up). Square root transformation of the variables was performed, if the assumptions for MLMA could not be achieved [25]. For those outcomes that yielded overall statistical significance (i.e., group x time interactions), univariate analysis of (co-)variance was conducted to determine if the group differences were observed at 12 week and/or 24 week follow-up [25]. The magnitude of statistically significant group differences was expressed in terms of Cohens d-statistic [26]. An effect size of 0.20 was considered small, 0.50 moderate and 0.80 large [26]. Non-parametric tests (Wilcoxon) were performed for those outcomes that did not fulfil the assumptions for MLMA [25]. A p-value less than or equal to 0.05 was considered significant. In order to limit the possibility of type 1 errors due to multiple testing, *p* values were Sidak-adjusted. In practice, this meant that a p-value less than or equal to 0.01 was considered significant [27]. The p-values for the secondary outcomes were not adjusted. The statistical analysis was carried out on an intention-to-treat basis. For all statistical tests, SPSS 18.0 (SPPS Inc, Chicago, IL) was used.

Results

Patients were enrolled from January, 2005 to November, 2008. We recruited 131 of 319 screened (41.1%) and 131 of 230 (56.9%) eligible patients (Figure 1). One hundred twenty-two patients were recruited from the University Hospital Zurich and 9 from the Cantonal Hospital St. Gallen. Reasons for ineligibility (n=89) were medical condition (n = 56), insufficient understanding of the German language (n=17), participation in another physical exercise program (n=5), mental retardation (n=1) and imprisonment (n=1). Nine patients (n = 9) were very anxious about the imminent SCT. We appraised that participating in a study would increase the level of stress in these patients; therefore, they were excluded from the study. Reasons for declining to participate (n= 99) were lack of interest (n=60), travel distance (n=15), being too busy (n=13), and unwillingness to be randomized (n=3). Eight patients did not indicate why they chose not to participate.

One hundred thirty-one patients were randomly assigned to the PE (n=64) or CG (n=67) group. No significant differences were observed between groups for any sociodemographic or clinical characteristics at baseline (table 1).

We obtained complete baseline data for all patients, with the exception of walking activity (n=102). Follow-up data were available for 114 patients (87%) at program completion and 105 patients (80%) at 3-month follow-up. There were no significant between-group differences at baseline for any of the objective or self-reported measures.

Compliance with the PE program and loss to study follow-up

Reasons for drop-out of patients in the PE group and in the CG are given in the flow chart (figure 1). Seven patients (10.9%, 4 men and 3 women), discontinued the PE program and were lost to follow-up. The average participation in the PE program was 85% (range 21% to 100%). This represents approximately 20.5 of 24 training sessions. Seven patients (10.9%) in the PE group reported $\geq$ 4 hours of intensive physical exercise per week. Five patients (7.5%) in the CG reported undergoing supervised physical exercise, at their own initiative, at a level comparable to the program of the PE group (i.e., 3 hours of aerobic exercise per week).
No adverse reactions or injuries were observed or reported as a result of either the assessments or the physical exercise intervention.

Effects on primary outcomes

Table 2 displays the effects of the program on physical performance outcomes, and indicates the covariates used in the models. MLMA showed significant interactions between group and time for knee-strength (p = .008, 95% CI -22.83 to -3.52), walking speed (p = .000, 95% CI .22 to .60) and functional exercise capacity (p = .011, 95% CI -32.4 to -4.4). No significant group x time interaction was observed for grip strength (p = .624, 95% CI -1.04 to .62). Planned contrast showed knee extension strength (p = .001), walking speed (p = .007) and functional exercise capacity (p = .007) improved after the PE intervention, compared to the UCG from baseline to 12 weeks. From baseline to 3 months follow-up, the PE group was superior to the UCG for knee strength (p = .000). The observed difference between groups for walking speed (p = .02) and functional exercise capacity (p = .02) was no longer statistically significant. The ES for the physical performance values varied between .56 and .69. Although decreasing slightly after 3 months (varying between .54 and .56), ES still indicated moderate treatment effects for knee extension strength and the 6-MWT (table 2).

There were no significant differences observed between the PE group and the UCG for the EORTC QLQ C-30 physical function subscale (table 3), between baseline and after completion of the program (p= .38), nor between baseline and follow-up (p = 0.03).

Effects on secondary outcomes

No statistically significant group x time interactions were observed for body composition (p- values varying from .240 to .455, table 4)**,** quantified walking activity (p- values varying from

.095 to.108, table 5), self-reported physical activity (p = 0.763, table 5) or fatigue (p = .056, table 5). For MLMA, the p-values for the secondary HRQOL outcomes varied between .157 and .850 (table 6). The covariates used in the models are indicated in the footnotes of tables 4-6.
The p-values for those outcomes that were analyzed with the Wilcoxon tests are reported in table 7. There was a statistically significant difference between groups for diarrhea (p = .01) and emotional functioning (p = .02) after completion of the program.

Discussion

The PE program yielded significant benefit in terms of physical performance outcomes, both at immediate post-program and at 3-month follow-up assessment. These effects were of a moderate magnitude. Compared to baseline, the mean changes in knee strength were 40.6 Nm (after completion) and 42.7 Nm (at follow-up) for knee extension strength. All values exceeded the smallest detectable difference of 17.2 Nm for this strength measurement protocol [17].

Compared to baseline, walking speed in the PE group improved by 9.5% after program completion and 11.9 % at follow-up; the 6MWT distance increased by 14% and 17.7%, respectively. These findings are consistent with an earlier report in which walking speed and the 6-MWT improved by 12% and 14%, respectively, in a supervised exercise group of HSCT recipients [10].

The predicted 6-MWT [28] and grip strength [29] values for allogeneic SCT patients (n = 56) [30] prior to and after [31] (n = 44) HSCT, were compared to the baseline results of allogeneic SCT patients (n = 52) in our study. Prior to HSCT, the 6-MWT was reduced to less than 80% predicted in 32 patients (58%) and reduced to 60% predicted in 5 patients (9.6%) [30]. After HSCT [31], 17 patients (81%) performed less than 80% of the predicted 6-MWT value, compared to 12 patients (23%) in our trial, and 6 patients (29%) [31] performed less than 60% of the predicted value, compared to 1 patient (2%) in our trial.

Prior to HSCT [30], average grip strength was reduced to less than 80% predicted in 22 patients (39%) and reduced to 60% predicted in 8 patients (15%). After HSCT [31], 33 patients (75%) performed less than 80% of the predicted grip strength value, compared to 15 patients (30%) in our trial, and 21 patients (47%) performed less than 60% of the predicted value [31], compared to 23 patients (45%) in our trial.

In this RCT, improvement in muscular strength, walking speed and walking distance resulting from the PE program did not translate into improvements in laboratory-based measures, real-world functioning measures or patient–reported outcomes, except for an improvement in diarrhea and emotional functioning. In contrast to our results, two earlier RCT's of physical exercise following HSCT observed a significant benefit in terms of increased body-weight [32,33] and two RCT's reported significant effects for HRQOL, and for physical and emotional well-being [34,35]. Possible explanations for the discrepancy in outcomes observed

between studies could be methodological (e.g., difference in sample-size) and/or substantive (e.g., differences in program frequency and intensity) in nature.

Knee extension, walking speed and functional exercise capacity yielded statistical significance after the training program. The observed improvement in functional exercise capacity in the PE group is particularly notable, given the fact that 20 minutes of aerobic exercise twice weekly represents a 'minimal dose' (i.e., low frequency) of physical exercise that falls below the guidelines of the American college of Sports Medicine. The results of this study suggest that a graded, moderate PE intervention improves physical performance outcomes in de-conditioned patients. We suspect that the effects of a PE intervention program on patient-reported outcomes such as fatigue and HRQOL might be stronger if the frequency of the aerobic exercise training was increased from 2 to 3 times a week [35] and the duration was extended from 20 up to 45 minutes [36]. Interval training above the ventilatory threshold and above the $V0_2$peak in an advanced phase for fitter patients or in a follow-up PE intervention might further improve cardiovascular fitness [36].

The positive results of the physical performance measures in our study are consistent with recent high quality studies [8 -10], investigating the effectiveness of physical exercise interventions in HSCT patients. Contrary to our results, significant effects have been reported for physical activity level (p = .0001), weight (p = .004), percentage body fat (p = .0006), BMI (p = .0002), quality of life (p = .03) and fatigue (p = .003) in studies among patients with breast and prostate cancer [37]. Additionally, quantified walking activity has been reported to be enhanced in (breast) cancer patients who participate in a combined physical activity and counselling program [38].

In the current study, the PE program was individually-based. This approach was chosen to maximize the convenience of the program for the participants. However, group based physical training interventions have been shown to be effective in increasing cancer survivors' HRQOL [39]. This probably reflects the psychosocial benefits that can accrue when group cohesion is created, providing social support and positive social comparisons. Additionally, cancer patients and survivors indicate that exercising in groups can increase one's motivation to overcome their physical limitations [39].

The current study included both patients who had undergone allogeneic and autologous HSCT. In autologous HSCT, the myeloablative treatment is less intense and hospitalization is considerably shorter than is typically for allogeneic HSCT cases [1]. It has been suggested that such treatment differences should be considered when comparing interventions and outcomes [8]. However, the baseline variables donor-type, diagnosis and time interval between HSCT and study assessments were examined as possible confounders, and were found to be non-significant.

Several possible limitations of the study should be noted. First, the study included a relatively large number of outcome measures. Therefore, to minimize the chance of making a type I error, p-value adjustments for correlated outcomes were considered. An objection to p-value adjustments is that if the chance of making a type I error is reduced, the chance of making a type II error, which is no less important, may be increased [40]. Therefore, p-value adjustments were performed only among the primary outcomes.

Second, we did not perform a maximal graded exercise test administered by an exercise physiologist to determine the level of cardiovascular fitness. This is a more accurate measure of maximal oxygen consumption compared with the 6-minute walking test, which only provides an estimation of sub-maximal performance. Nevertheless, the 6 MWT-test showed an improvement immediately after program completion and at follow-up.

Third, the percentage of drop-outs at follow-up was almost 20%. While this is not a trivial percentage, it is lower than the attrition reported in other similar studies, ranging from 25% to 56% [2]. Third, although we were unable to document this due to limited access to data from study decliners, patients who were willing to participate in this study may have differed from those who declined participation in terms of such factors as age, education, earlier PE habits, fitness level, body mass index and resilience [15]. Future studies are needed to better understand why patients chose (not) to participate in PE programs, and how to improve recruitment rates [15].

Potential biasing effects may have affected the quantitative walking activity measurements, as patients may have increased their physical activity level simply by virtue of the fact that they knew that they were being monitored. However, this type of reactive effect is likely to have affected both the PE and UC groups [22]. Another possible reason why we were unable to detect a significant difference between groups for walking is that the PE group was not advised to achieve a specific step count (i.e. 10’000 steps /day) [22,41,42].

Conclusion

The results of our study indicate that physical performance, but not body composition, physical activity level in daily life, fatigue or HRQOL improves in HSCT recipients after a PE intervention. PE should be considered in the management of HSCT recipients after discharge from hospital. Additional efforts are needed to strengthen the effect of such programs, and to develop PE programs that attract a larger percentage of HSCT recipients.

Table 1. Baseline sociodemographic, clinical and behavioral profile of patients overall and by group assignment

	All (n=131)		PE (n=64)		UCG (n=67)		
	n	%	n	%	n	%	p-value
Age*							0.97
Mean	46.7		46.7		46.6		
SD	12.8		13.7		12.0		
Range	18-75		18-75		20-67		
Gender‡							0.89
Woman	54	41.2	26	40.6	28	41.8	
Man	77	58.8	38	59.4	39	58.2	
Marital status‡							0.15
Single	36	27.5	15	23.4	21	31.3	
Married / Partner	79	60.3	40	62.5	39	58.2	
Divorced	12	9.2	5	7.8	7	10.4	
Widowed	4	3.1	4	6.2	0	0	
Education‡							0.83
Secondary school	18	13.7	8	12.5	10	14.9	
Vocational	56	42.7	26	40.6	30	44.8	
Higher professional	21	16.0	12	18.8	9	13.4	
College / University	36	27.5	18	28.1	18	26.9	
Diagnosis‡							0.18
Leukaemia							
Acute myeloid leukemia	31	23.7	19	29.7	12	17.9	
Chronic lymphocytic leukemia	14	10.7	5	7.8	9	13.4	
Acute lymphoblastic leukemia	2	1.5	0	0	2	3	
Lymphoma							
Hodgkin	14	10.7	5	7.8	9	13.4	
Non Hodgkin lymphoma	25	19.1	11	17.2	14	20.9	
Multiple myeloma	37	28.2	17	26.6	20	29.9	
Osteomyelofibrosis	4	3.1	3	4.7	1	1.5	
Amyloidosis	1	0.8	1	1.6	0	0	
Testicular cancer	3	2.3	3	4.7	0	0	
Allogeneic/Autologous SCT-Type‡							0.45
Allogeneic	51	38.9	27	42.2	24	35.8	
Autologous	80	61.1	37	57.8	43	64.2	
Donor‡							0.53
Allogeneic							
Unrelated donor	30	22.9	17	26.6	13	19.4	
Related donor	21	16.0	10	15.6	11	16.4	
Autologous							
ASCT 1x	57	43.5	28	43.8	29	43.3	
ASCT 2x	22	16.8	8	12.5	14	20.9	
ASCT 3x	1	0.8	1	1.6	0	0	

PE, Physical exercise, UCG; Usual care group, ASCT, Autologous stem cell transplantation. Statistical testing at baseline was done with an independent Student's t-test* or Pearson X^2 test‡.

Table 1. Baseline sociodemographic, clinical and behavioral profile of patients overall and by group assignment (continued)

	All (n = 131)		PE (N = 64)		UCG (n=67		
	n	%	n	%	n	%	p-value
Conditioning for allogeneic patients (N) ‡							0.37
Full intensity	33	25.2	15	23.4	18	26.9	
Reduced intensity	17	13.0	11	18.2	6	9.0	
ASCT	80	61.8	38	59.4	43	64.2	
No. of patients in complete remission before HSCT*							0.98
Yes	49	29	24	37.5	25	37.3	
No	82	71	40	62.5	42	62.7	
TBI for allogeneic patients yes /no‡							0.76
	23	17.6	12	18.8	11	16.4	
	/108	82.4	/52	81.2	/56	83.6	
Series chemotherapy before HSCT‡							0.78
One	6	4.6	4	6.3	2	3.0	
Two	27	20.6	13	20.3	14	20.9	
Three	10	7.6	4	6.3	6	9.0	
Four or more	88	67.2	43	67.2	45	67.2	
Time interval (days) between HSCT and study assessments*							0.68
Mean		79		81		78	
SD		35		36		35	
Range		22-139		27-134		22-139	
BMI*							0.19
Mean		23.4		22.9		23.9	
SD		4.2		4.3		4.0	
Range		14-38		15-38		14-34	
Leisure time physical activity‡							0.19
Almost completely inactive	44	33.6	25	39.1	19	28.4	
Minimum 20 minutes walking/cycling/day	87	66.4	39	60.9	48	71.6	

PE, Physical exercise, UCG; Usual care group, ASCT, Autologous stem cell transplantation. Statistical testing at baseline was done with an independent Student's t-test* or Pearson X^2 test.

Table 2. Effects on primary physical performance measures

	Baseline		**At program completion**		**At follow-up**		**G x T**	**95% CI**	**From baseline to program completion**		**From baseline to follow-up**	
Outcome measure	PE	UCG	PE	UCG	PE	UCG	p-value	UB LB	p	*d*	p	*d*
Knee ext (Nm) Mean	162.8	153.4	203.4	162.0	205.5	172.1	.008	-22.83 -3.52	.001	.69	.000	.56
SD	54.9	51.1	61.5	58.4	55.8	63.7						
Grip (Kg) Mean	34.0	33.8	36.5	34.4	36.5	36.0	.624	-1.04 .62	.30	.21	.61	.02
SD	10.2	8.6	10.9	9.5	11.8	10.5						
Walking speed (Sec) Mean	8.4	8.5	7.6	8.5	7.4	8.3	.000	.22 .60	.007	.56	.02	.56
SD	1.5	1.5	1.7	1.5	1.7	1.5						
6-MWT (m) mean	581.3	570.1	665.5	609.9	684.4	626.2	.011	-32.4 -4.4	.007	.56	.02*	.54
SD	92.8	82.2	100.8	96.5	119.2	94.2						

For baseline data, after program completion and follow-up, raw unadjusted means are shown. The covariates used in the model for knee extension, grip strength, walking speed and 6-MWT were age, gender, type of stem cell transplantation-type and body mass index. Physical performance measures are primary outcomes (Sidak-adjusted p-value = 0.01). All planned contrasts were performed with univariate analyses of co-variance, except for the 6-MWT* (from baseline to follow-up) that was performed with univariate analyses of variance.
Abbreviations: PE; Physical exercise, UCG; Usual care group, G x T; Group x time intervention, UB; Upper boundary, LB; Lower boundary, *p;* p-value, *d* = effect size.
Knee ext; Knee extension, Nm; Newton-meter, Kg; Kilogram, Walking speed; 50 foot walking at fastest speed test, Sec; seconds, 6-MWT; 6 minute walking test, m; meters.

Table 3. Effects on HRQOL (primary outcome physical-functioning)

	Baseline		At program completion		p-value	At follow-up		p-value
Outcome	PE	UCG	PE	UCG		PE	UCG	
Physical function								
Median	73.3	66.7	86.7	86.7	.38	93.3	86.7	.03
Mean	71.9	67.8	83.7	80.4		87.4	82.4	
SD	18.0	17.0	14.2	14.0		14.1	15.7	

For baseline data, after program completion and follow-up, raw unadjusted means are shown, Sidak-adjusted p-value = 0.01.The analysis was performed with a non-parametric test (Wilcoxon). PE; Physical exercise, UCG; Usual care group.

Table 4. Effects on body composition

	Baseline		At program completion		At Follow-up		Group x time interaction	95% CI
Outcome measure	PE	UCG	PE	UCG	PE	UCG	p-value F-value	LB UB
Weight								
Mean (Kg)	70.2	72.8	70.8	72.5	70.0	71.4	.455	-.55
SD	15.1	13.6	14.5	13.8	13.6	14.4	.56	1.23
Fat mass								
Mean (Kg)	18.8	20.0	18.3	19.6	18.0	21.3	.240 1.38	-0.42 1.71
SD	7.3	7.4	7.0	7.4	5.9	8.4		
Lean mass								
Mean (Kg)	50.9	51.7	52.2	52.0	50.6	52.0	.286 .78	-0.51 0.68
SD	10.9	10.5	11.1	10.9	11.2	11.4		

For baseline data, after program completion and follow-up, raw unadjusted means are shown. The covariates used in the analyses were time, gender and body mass index. PE; Physical exercise, UCG; Usual care group, LB; Lower bound, UB; Upper bound.

Table 5. Effects on quantified walking activity, self-reported physical activity and fatigue

	Baseline		At program completion		At follow-up		Group x time interaction	95% CI
Outcome measure	PE	UCG	PE	UCG	PE	UCG	p-value F-value	LB UB
Quantified walking activity (SAM)								
Average Steps*							.108 2.61	-.49 4.93
Mean	4924	4492	5099	5023	5102	5264		
SD	1790	1897	1493	2062	1828	2261		
Peak activity							.095 2.83	-22 2.75
Mean	42.3	41.3	43.9	42.6	42.0	44.0		
SD	7.0	7.7	5.9	9.0	7.6	8.8		
Self-reported physical activity (IPAQ)								
Total activity met-min/wk*							.763 .091	-1.04 3.45
Mean	6735	6058	9738	8303	10343	9039		
SD	5817	5377	6699	9470	7408	7900		
Fatigue (FACT-An)								
FACT-An							.056	-.04
Mean	35.9	32.8	43.6	40.0	42.3	41.9	3.70	3.29
SD	10.3	9.2	8.4	7.5	9.1	7.3		

For baseline data, after program completion and follow-up, raw unadjusted means are shown.
*Outcomes were transformed; however, raw data were presented for use of interpretation.
The covariates used in the analyses for quantified walking were gender and leisure time physical activity. The covariate used in the analyses for self-reported physical activity and self-reported fatigue was leisure time physical activity. PE; Physical exercise, UCG; Usual care group, LB; Lower bound, UB; Upper bound, SAM; Step activity monitor, IPAQ; International physical activity questionnaire; FACT/AN; Functional Assessment of Cancer Therapy /Anaemia Scale.

Table 6. Effects on secondary HRQOL outcomes (Results of mixed linear model analyses)

	Baseline		At program completion		At follow-up		Group x time interaction	95% CI
Outcome measure	PE	UCG	PE	UCG	PE	UCG	p-value F-value	LB UB
Role function							.527 .401	-3.76 7.34
Mean	52.3	44.8	68.7	61.3	76.3	70.2		
SD	31.0	26.1	24.2	26.0	26.9	25.2		
Cognitive function							.685 .165	-4.48 2.95
Mean	79.7	76.6	87.6	79.2	85.6	78.9		
SD	18.2	19.9	16.7	21.1	17.8	20.7		
Social function							.850 .036	-5.83 4.81
Mean	56.8	57.0	71.3	72.9	78.5	75		
SD	29.9	24.6	28.6	24.9	26.3	25.5		
GHS							.731	-2.88
Mean	62.8	58.2	73.7	67.7	72.9	69.6	.118	4.09
SD	17.5	14.8	14.9	15.7	17.2	16.8		
Fatigue							.157	-8.01
Mean	47.6	54.6	31.6	38.3	30.1	32.1	2.014	1.30
SD	25.5	22.9	22.1	20.0	24.9	19.1		
Pain*							.467	-.26
Mean	24.0	26.4	17.8	26.8	21.2	19.9	.533	12
SD	27.5	27.9	27.1	28.4	30.6	24.9		
Insomnia*							.592	-.97
Mean	30.2	34.3	23.0	31.5	26.3	25.0	.289	.55
SD	30.1	31.2	27.4	30.8	31.9	30.9		

For baseline data, after program completion and follow-up, raw unadjusted means are shown. *Outcomes were transformed; however, raw data were presented for use of interpretation.
The covariates used in the analyses for HRQOL-models were age, gender, marital status, level of education and leisure time physical activity. LB; Lower bound, UB; Upper bound, PE; Physical exercise, UCG; Usual care group, GHS; General Health Score.

Table 7. Effects on secondary HRQOL outcomes (Results of non-parametric tests)

	Baseline		At program completion		p-value	At follow-up		p-value
Outcome	PE	UCG	PE	UCG		PE	UCG	
Emotional function								
Median	75.0	66.7	83.3	75.0	.02	83.3	75.0	.07
Mean	73.6	69.3	76.1	72.6		75.6	76.4	
SD	24.2	18.5	24.9	22.2		24.2	18.5	
Nausea Vomiting								
Median	0	0	0	0	.30	0	0	.46
Mean	10.9	14.4	3.7	6.5		3.8	4.8	
SD	16.0	19.9	9.9	13.4		9.7	10.1	
Dyspnea								
Median	33.3	33.3	33.3	33.3	.39	0	33.3	.43
Mean	34.4	43.8	21.8	29.2		19.2	25.6	
SD	33.1	29.7	24.6	23.0		24.1	25.2	
Appetite								
Median	0	33.3	0	33.3	.90	0	33.3	.48
Mean	22.9	28.9	8.6	10.7		11.5	6.4	
SD	30.2	30.1	17.2	22.1		22.8	13.3	
Constipation								
Median	0	0	0	0	.09	0	0	.43
Mean	4.7	7.0	4.6	7.7		7.1	5.8	
SD	14.4	17.0	17.0	16.8		15.2	15.8	
Diahrrea								
Median	0	0	0	0	.01	0	0	.17
Mean	13.0	18.4	8.6	18.5		9.6	11.5	
SD	23.5	23.4	18.3	24.6		23.2	18.5	
Financial								
Median	0	0	0	0	.19	0	0	.09
Mean	17.7	19.4	14.4	18.5		12.8	21.2	
SD	30.3	25.4	27.3	27.6		25.7	29.5	

For baseline data, after program completion and follow-up, raw unadjusted means are shown. Outcomes were analyzed with a non-parametric test (Wilcoxon). PE; Physical exercise, UCG; Usual care group.

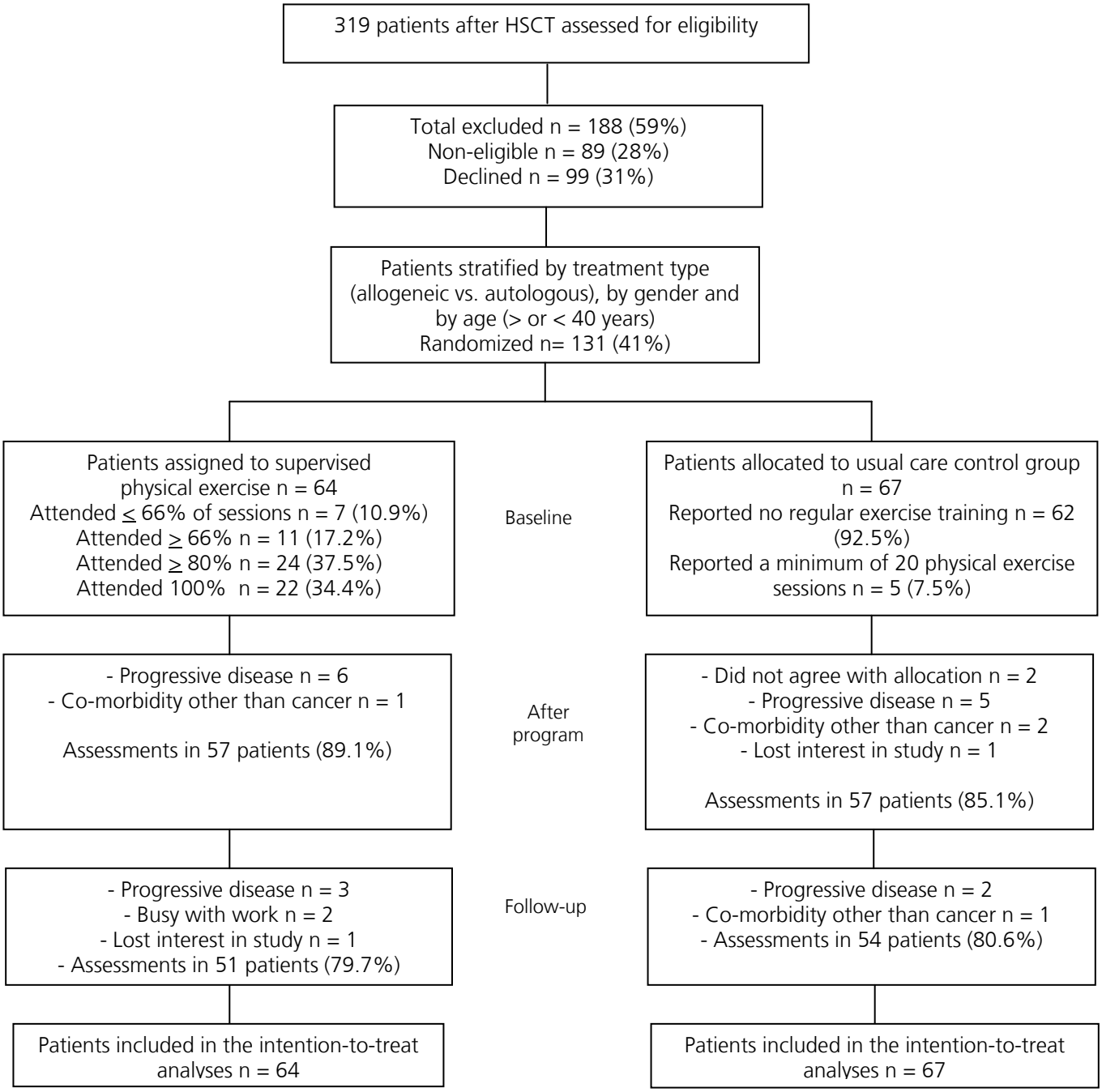

Figure 1. Consort diagram showing flow of the participants through the trial.

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