Bone Marrow Transplantation (2014) **49**, 443–448
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ORIGINAL ARTICLE

Efficacy of exercise training in SCT patients-who benefits most?

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Patients undergoing allo-HCT often experience a substantial loss in physical performance. We have recently published the general effectiveness of an exercise intervention in 105 allo-HCT patients on physical performance and psychosocial well-being. However, predictor variables for differentiated treatment response remained unclear. To determine the impact of basic physical performance on treatment response, we assessed muscle strength and endurance performance at four assessment points before and after allo-HCT. The exercise group started training 2 weeks before admission and ended 6–8 weeks after discharge. Comparing initially *fit* with *unfit* classified patients, the *fit* patients lost 31% of the strength of the knee-extensors, whereas the *unfit* patients lost only 1% ($P<0.05$). For endurance capacity, *fit* patients lost 4% of their walking capability, whereas *unfit* patients gained 13% ($P<0.05$). The individual percent change was statistically different at the 0.05 level in all measures of physical performance. Individual training response in allo-HCT patients strongly depends on the initial physical performance level. *Unfit* patients can be trained safely and may benefit more from this exercise intervention than fit patients. This result is of major clinical relevance and should encourage hematologists to promote exercise even more in impaired/unfit allo-HCT patients.

Bone Marrow Transplantation (2014) **49**, 443–448; doi:10.1038/bmt.2013.194; published online 9 December 2013

Keywords: cancer; physical activity; fitness; endurance; strength; oncology

INTRODUCTION

Allo-HCT is an effective medical treatment option for patients with high-risk hematological malignancies such as acute leukemia. However, patients may suffer from numerous treatment-related side effects and complications, for example, infections, GVHD and TRM rate is considerable.[1] Before allo-HCT, patients' physical performance is already affected due to the disease itself and prior treatment.[2,3] Physical inactivity, resulting from long hospitalization and side effects or complications, leads to an additional loss of physical performance. A recent review shows that patients after HCT are likely to have long-term difficulties with physical functioning, fatigue, distress and psychological well-being.[4] Particularly after allo-HCT patients are at high risk because of a high prevalence of chronic GVHD, which is associated with a lower physical performance and functional capacity.[5]

In recent years, several clinical trials have contributed to the growing body of evidence about the beneficial effects of exercise in cancer patients; some general exercise recommendations for cancer patients have already been published.[6] Our group reviewed exercise intervention studies in the context of HCT and illustrated that exercise interventions can significantly improve physical performance, quality of life and fatigue at different time points during and after HCT.[7] Since this review, six new randomized controlled trials have been published, supporting these findings; some studies showed strong effects for body composition as well as weaker but promising effects for cardiorespiratory fitness, fatigue, muscle strength, physical functioning and quality of life.[8–13]

Nevertheless, many questions remain unanswered regarding exercise interventions in HCT patients. Additional evidence is required to determine the optimal exercise recommendation, with respect to amount, type, intensity and time point for intervention. Furthermore, the exercise response among patients of different baseline fitness levels has not been defined and is critical to make personalized treatment decisions.

In healthy populations, the initial level of fitness appears to determine the physiological training response with greater potential in increase among the initially unfit. For example, the HERITAGE Family Study investigated intra-individual variation in responsiveness to regular exercise training in healthy, sedentary individuals and showed that lower initial fitness values were associated with greater relative changes.[14] There are only few studies that have investigated the response to an exercise program with respect to initial fitness level in diseased individuals. A study among cystic fibrosis patients showed that a 6-week exercise program led to significantly different training responses between initially fit and unfit groups, with greater improvements in subjects with a lower initial fitness level.[15] To our knowledge, no information is available concerning the benefits of an exercise program in relation to initial fitness level among HCT patients.

Previously, we demonstrated within a randomized controlled trial that a partly self-administered exercise intervention prior, during and after allo-HCT is able to improve fatigue, physical performance and functioning as well as psychological distress and other treatment-related side effects.[13] Here, we further define the individual training response of the exercising patients with respect to initial fitness performing *post hoc* analysis. To analyze the individual training response, we classified patients who were randomized to exercise (EX) in either a *fit* or an *unfit* group and measured both endurance capacity and muscle strength.

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Received 22 June 2013; revised 12 October 2013; accepted 17 October 2013; published online 9 December 2013

PATIENTS AND METHODS

Design

Our study was a prospective, multicenter randomized controlled trial in allo-HCT patients in Germany. Of 112 initially recruited patients, 105 started and 80 completed the study. A detailed description of the demographics of the participants and patient flow is described elsewhere.[13] Briefly, patients were randomized by the minimization procedures and stratified by age, disease and sex for each center. Recruitment and randomization took place 1–4 weeks before admission to hospital. All patients provided written informed consent and all procedures were approved by the Ethics Committee II of the University of Heidelberg/Mannheim and the Physician Board Hessen.

Patients who were randomized to EX started a self-directed, home-based exercise program 1–4 weeks before hospital admission. After admission, they continued training at the hospital. In this phase, the exercise training was supervised 2 × /week by an exercise therapist. After discharge, patients continued with up to 8 weeks of self-directed, home-based exercise training. At the beginning of the intervention, patients were provided with an introduction to the exercise protocol and received an individualized exercise manual (including DVD). During the outpatient period, participants were called weekly to review adherence to the intervention and identify problems in the EX. The intervention consisted of a combination of endurance and resistance exercises using stretch bands (3–5 × /week endurance, 2 × /week resistance training). A single session lasted 20–40 min. We developed a system by which patients can rate their daily clinical and psychological status, which we in turn used to tailor exercise intensity. Contraindications for exercise were plt counts below 10 000/μL, signs of bleeding, Hb level below 8 g/dL, infections with fever > 38 °C, severe pain, nausea or dizziness.

Patients assigned to the control group were informed that moderate physical activity is recommended during the entire transplantation process, but were not given any further exercise recommendations or instructions. To avoid socio-psychological bias, patients in the control group received the same frequency of social contact (for example, telephone calls and visits in hospital) as the exercise group.

Outcomes

All outcomes were measured at four time points during the transplantation process. Baseline measurements (t_0) were obtained 1–4 weeks before admission, t_1 at the day of admission, t_2 at the day of discharge and t_3 6–8 weeks after discharge (see Figure 1).

Maximal voluntary isometric strength was measured in Newton (N) by a hand-held dynamometer (C.I.T. Technics, Groningen, The Netherlands). Hand-held dynamometers have previously been used in hematological cancer patients, have proven to be reliable and are well tolerated.[16,17] Within standardized test positions,[18] we assessed seven different muscle groups, including knee-extensors, knee-flexors, hip-abductors, hip-flexors, elbow-extensors, elbow-flexors and shoulder-abductors of the dominant and non-dominant side. Patients were advised to start with low force, and then quickly raise the force to their maximum, and to hold it for 3 s. Each measurement was repeated three times. Values < 10% different from the median were excluded.

Endurance performance was measured by the 6-min walk test.[19,20] The 6-min walk test is a submaximal performance test that reflects the tasks of daily living and has previously been used in hematological cancer populations.[3,9] Patients were advised to walk back and forth down a hallway as fast as possible for 6 min. The 6-min walk distance (6MWD) was assessed in meters (m). Heart rate was measured before, during and after the test. Additionally, the individual perceived exhaustion was assessed using the BORG Scale.[20]

Besides physical performance parameters, we also assessed patient-related outcomes (PROs) as follows: fatigue was assessed with the MFI-20,[21] quality of life with the EORTC QLQ-30,[22] and Distress with the NCCN Distress Thermometer.[23] All questionnaires are widely used in cancer populations.

Statistical analysis

After tests for normality, χ^2 tests, Fisher's exact test and Student's *t*-test were used to compare group characteristics. ANOVA with repeated measurements including the Levene statistic for testing homogeneity of variances was used for group comparisons. If necessary, the Greenhouse-Geisser correction was applied. We calculated the percent change from baseline to end of intervention (t_0–t_3) for *fit* and *unfit* comparison. For 3-group comparisons (EX fit, EX unfit and controls), we conducted an ANOVA and defined contrasts. We furthermore controlled for age by performing an analysis of covariance. The significant level was set at $\alpha < 0.05$. All statistical analyses were performed using SPSS (German Version 19.0 for Windows, IBM corporation, Armonk, NY, USA).

Patients in EX were classified depending on the baseline assessment in either *fit* or *unfit* categories, specifically for each fitness parameter. For muscle strength, patients were classified as *fit* when they reached a minimum of 80% of their age- and gender-specific norm value by Bohannon *et al.*[18] Patients who reached < 80% were classified as *unfit*. Due to missing norm values for knee-flexion, hip-abduction and shoulder abduction we did not include these measurements in our analyses. For endurance capacity, the classification procedure was the same (⩾80 vs < 80%) with respect to the predicted individual norm value, calculated by the gender-specific equations of Enright.[24]

RESULTS

Demographic and medical characteristics of study participants are described in Table 1. More detailed information is given elsewhere.[13] Patient characteristics grouped by *fit* and *unfit* showed that there were no significant differences in sex, age, Karnofsky score, disease risk, intensity of conditioning and HLA-match/mismatch. Exceptions were the knee-extensor strength and walking distance where initially unfit patients were significantly

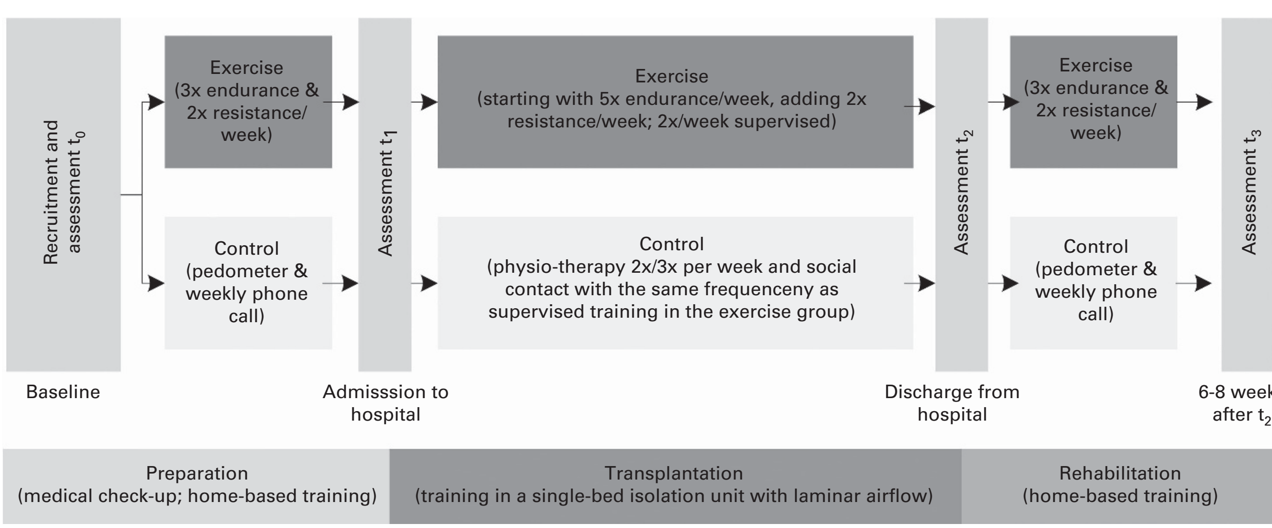

Figure 1. Study design[13] (with permission from the journal *Blood*).

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Table 1. Baseline medical and demographic characteristics

	All (n = *105*)	*Exercise* (n = *52*)	*Control* (n = *53*)	P-*value*
Center				
Heidelberg	25	13	12	
Wiesbaden	80	39	41	
Age (mean, range)	48.8 (18–71)	47.6 (18–70)	50 (20–71)	*0.38*
Gender (male/female)				*0.10*[a]
Male (%)	71	32 (45)	39 (55)	
Female (%)	34	21 (62)	13 (38)	
Karnofsky score t_0 (median)	90	90	90	*0.40*[b]
90–100	82	43	39	
80–90	20	7	13	
<80	3	2	1	
BMI (mean, s.d.)	24.9 (4.1)	25.1 (4.3)	24.7 (3.9)	*0.66*
Diagnosis				
AML	22	12	10	
ALL	14	6	8	
CML	4	2	2	
CLL	4	2	2	
MDS	12	7	5	
Sec. AML	11	6	5	
MPS	13	7	6	
Multiple myeloma	3	2	1	
Other lymphomas	20	7	13	
Aplastic anemia	2	1	1	
Source of stem cell				*1.0*[a]
BM	15	7	8	
Peripheral blood cells	90	45	45	
Donor–recipient characteristics				*0.49*[a]
HLA-ident (related)	28	13	15	
HLA-matched/ unrelated	56	26	30	
HLA-mismatched/ unrelated	21	13	8	
Intensity of conditioning				*0.82*[a]
Myeloablative	24	11	13	
Reduced intensity	81	41	40	

Abbreviations: ALL = acute lymphoblastic leukemia; AML = acute myeloid leukemia; BMI, body mass index; CLL = chronic lymphocytic leukemia; CML = chronic myeloid leukemia; HLA = human leukocyte antigen; MDS = myelodysplastic syndrome; MPS = myeloproliferative syndrome. [a]Fisher's exact test. [b]Wilcoxon test.

younger (43.9 ± 14.5 vs 57.5 ± 15.03 years for knee-extensor and 35.2 ± 14.7 vs 52.8 ± 12.8 years for 6MWD). Overall, exercise adherence was 87% (85, 83 and 91% before, during and after transplantation, respectively). We observed no difference in exercise adherence between EX *fit* (86%) and EX *unfit* (89%) patients. Furthermore, the presence of co-morbidities in the *fit*, *unfit* and control group was comparable. In all, 27.3% of the EX *fit*, 17.2% of the EX *unfit* and 30.8% of the controls reported cardiologic co-morbidities (for example, hypertension and coronary heart disease). With regard to orthopedic co-morbidities, 9.1% of the EX *fit*, 13.8% of the EX *unfit* and 17.1% of the controls reported the presence of, for example, a disc prolapse. Psychological disorders were present in one patient (2.6%) in the control and three patients (10.3%) in the EX *unfit* group. Finally, one patient (3.4%) in the EX *unfit* and four patients (10.3%) in the control group reported the presence of diabetes mellitus type II.

Training response in EX fit and EX unfit

We observed a stronger benefit of the exercise intervention in initially *unfit* patients compared with *fit* patients for all measured muscle strength groups (all $P < 0.05$), with less loss or even gain over the transplant period (Table 2). With respect to endurance performance, a significantly better training response in *unfit* patients (13.4 vs −3.7%; $P < 0.01$) for the 6MWD was observed (Figure 2). Furthermore, we detected significant interactions (time × group (fit/unfit)) in the age-adjusted analysis of covariance for changes in knee-extensor strength ($P = 0.02$) and the 6MWD ($P = 0.02$), illustrating that knee-strength and endurance development are independent with respect to participant age (Table 2). For hip-flexion, elbow-extension and elbow-flexion, similar effects were observed with *P*-values for the fit/unfit interaction ranging from $P = 0.051$ to 0.054.

Training response compared with controls

Comparing the percent changes with the control group (EX *fit*, EX *unfit* and controls), we found significant different group developments for all measurements, except for the elbow flexors, suggesting a significantly different fitness development in the groups. We observed that the initially *unfit* patients developed significantly better than the initially *fit* patients and the controls over study time. This was true again for all muscle groups and the 6MWD with the exception of elbow flexors. There was no difference in the percent change between the *fit* patients and the CG (see Table 3).

Figure 3 illustrates the development of knee-extensor strength and 6MWD for EX *fit*, EX *unfit* and controls over study time.

Changes in PROs

We have also investigated whether the different development of physical performance parameters in the EX *fit* and EX *unfit* are related to comparable changes in PROs. Results showed that there were no significant changes with regard to PROs. Nevertheless, we found non-significant changes favoring the EX *unfit* in comparison with the Ex *fit* group with regard to general fatigue (−9.5 vs −1.4%; n.s.), quality of life (5.0 vs −3.5%; n.s.), physical functioning (0.5 vs −8.0%; n.s.) and distress (−35.5 vs −28.2%; n.s.).

DISCUSSION

Our study demonstrates that the individual training response in patients undergoing allo-HCT depends on the initial performance level. After stratifying by baseline fitness levels before transplantation, we demonstrate that the training response to the partly supervised exercise intervention was superior in *unfit* patients compared with *fit* patients. This implies that particularly *unfit* patients benefited more from our program than did *fit* patients.

Even if we cannot find a significant relation to PROs like fatigue, quality of life and distress, these findings are of high clinical relevance because exercise is often not recommended for patients with poor health status in clinical practice. Physicians as well as nurses and exercise-/physiotherapists tend to recommend rest in such situations. In contrast, our results indicate that particularly unfit or weak patients will benefit from an individually adapted exercise program; thus, for this patient group exercising should be strongly recommended.

As expected, patients were not able to increase the physical fitness in the context of an intensive medical treatment, such as

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Table 2. Comparison of muscle strength and endurance performance in initially fit (EX *fit*) and unfit (EX *unfit*) of the exercise group over study time

	EX fit vs EX unfit				*Group comparison*		
Variable	t_0	t_1	t_2	t_3	*Change (T_0–T_3)*		*ANOVA/ANCOVA*
	mean (s.d.)	*mean (s.d.)*	*mean (s.d.)*	*mean (s.d.)*	%	P-*value*	
Knee-extension							
EX fit $n=11$	326 (53)	268 (73)	231 (69)	224 (73)	− 31.1	0.03*	Time ($P=0.05$)* Interaction ($P=0.02$)* Group ($P=0.47$) Age ($P=0.24$)
EX unfit $n=28$	257 (93)	293 (149)	234 (104)	235 (92)	− 1.7		
Hip-flexion							
EX fit $n=29$	171 (50)	164 (57)	153 (59)	143 (47)	− 13.0	0.03*	Time ($P=0.34$) Interaction ($P=0.051$) Group ($P=0.17$) Age ($P=0.44$)
EX unfit $n=10$	128 (35)	162 (63)	153 (70)	135 (47)	10.3		
Elbow-extension							
EX fit $n=29$	156 (51)	151 (51)	135 (56)	123 (41)	− 17.0	0.04*	Time ($P=0.62$) Interaction ($P=0.054$) Group ($P=0.34$) Age ($P=0.37$)
EX unfit $n=10$	124 (29)	140 (51)	130 (35)	128 (41)	3.4		
Elbow-flexion							
EX fit $n=24$	204 (65)	208 (66)	172 (71)	159 (43)	− 18.1	0.05*	Time ($P=0.39$) Interaction ($P=0.052$) Group ($P=0.37$) Age ($P=0.41$)
EX unfit $n=15$	172 (33)	187 (54)	161 (40)	164 (42)	− 4.4		
Distance 6MWT							
EX fit $n=28$	556 (78)	563 (82)	470 (86)	532 (86)	− 3.7	<0.01**	Time ($P=0.43$) Interaction ($P=0.03$)* Group ($P=0.34$) Age ($P=0.30$)
EX unfit $n=11$	501 (102)	535 (102)	482 (98)	553 (63)	13.4		

Abbreviations: 6MWT = 6-min walk test; ANOVA; analysis of variance; ANCOVA = analysis of covariance. *$P=<0.05$. **$P=<0.01$.

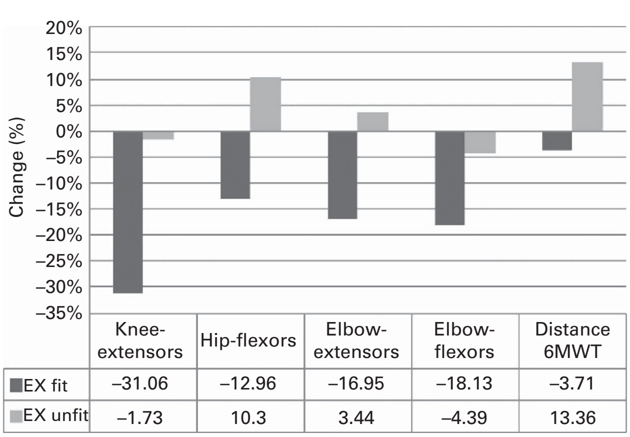

Figure 2. Baseline-stratified changes for different muscle groups and 6-min walk distance in initially *fit* and *unfit* patients. EX fit = initially fit patients in the exercise group; EX unfit = initially unfit patients in the exercise group.

allo-HCT. Overall, we did not observe any gain in muscle strength in the *fit* or *unfit* group during the overall course of the study. Only a small non-significant increase (+10%) in one measured muscle group (hip-flexor) was seen in the *unfit* group. Comparable results were reported by others[10,25] showing that exercising under allo-HCT can prevent the loss of physical performance, but does not result in increases. Furthermore, the study by Defor *et al.*[26] also showed comparable results with regard to the Karnofsky performance score. The author found that their 100-day endurance program significantly increased Karnofsky performance score in the subset of patients who received non-myeloablative treatment indicating a group of older and potentially unfit patients.

With regard to the differential development between the *fit* and *unfit* groups in our study, one could speculate that for the initially *fit* patients, the intensity of the prescribed exercise was too low, whereas this intensity might have been the appropriate amount for the initially *unfit* patients. There were no differences in adherence between the two groups eliminating this as a potential explanation.

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Table 3. Comparison of change in muscle strength and endurance performance in initially fit (EX *fit*), unfit (EX *unfit*) and controls over study time

3-Group comparison (ANOVA)		
EX fit/EX unfit/controls	*ANOVA comparison %-change t_0–t_3*	
Knee-extension (*n* = 11/28/38)	Group (*P* = 0.02)*	Fit vs controls (*P* = 0.23) Unfit vs controls (*P* = 0.03)* Fit vs unfit (*P* < 0.01)**
Hip-flexion (*n* = 29/10/38)	Group (*P* < 0.01)**	Fit vs controls (*P* = 0.31) Unfit vs controls (*P* < 0.01)** Fit vs unfit (*P* = 0.01)*
Elbow-extension (*n* = 29/10/38)	Group (*P* = 0.02)*	Fit vs controls (*P* = 0.64) Unfit vs controls (*P* < 0.01)** Fit vs unfit (*P* = 0.01)**
Elbow-flexion (*n* = 24/15/38)	Group (*P* = 0.09)	Fit vs controls (*P* = 0.56) Unfit vs controls (*P* = 0.07) Fit vs unfit (*P* = 0.03)*
Distance 6MWT (*n* = 28/11/38)	Group (*P* < 0.01)**	Fit vs controls (*P* = 0.13) Unfit vs controls (*P* < 0.01)** Fit vs unfit (*P* < 0.01)**

Abbreviations: 6MWT = 6-min walk test; ANOVA; analysis of variance. **P* = < 0.05. ***P* = < 0.01.

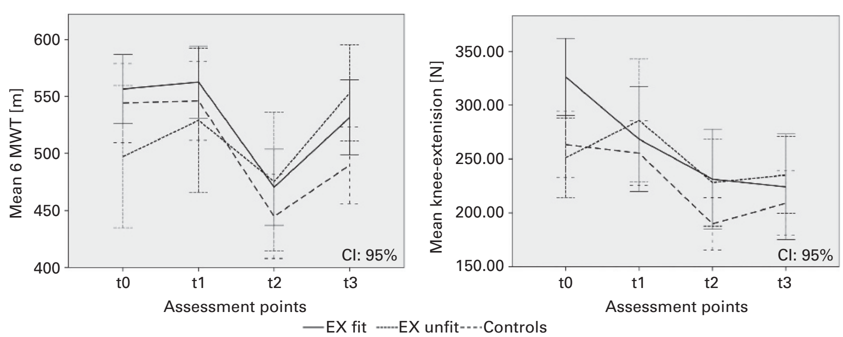

Figure 3. Development of 6-min walk distance (left) and knee-extension muscle strength (right) for initially fit and unfit exercising patients and for controls. EX fit = initially fit patients in the exercise group; EX unfit = initially unfit patients in the exercise group.

The 'inappropriate intensity explanation' for the *fit* patients in the exercise group is supported by the observation that there is no differential physical performance development between this group and the controls. However, the *fit* group maintained a higher performance level during the entire intervention period and had therefore a much better physical performance outcome than the controls. Nevertheless, a better development of physical performance in exercising patients should be expected when comparing them with a non-exercising control group, even if they have comparable age- and gender-specific levels of physical fitness before the transplantation process.

Beside the 'inappropriate intensity explanation' there are several reasons that could explain the observation of the similar fitness development between the *fit* exercising and the control patients. It is important to consider that our controls were quite active due to the general recommendation to stay active during the transplant and isolation period. We previously published pedometer data and showed that there were no significant differences in step count between exercising and control patients.[13] Pedometers and general exercise recommendations are known to enhance physical activity/walking time in cancer patients,[27] which may have also influenced our results. Controls also had access to exercise equipment (for example, bicycle ergometers, treadmill and free weights) during the in-patient setting. Finally, controls also received physiotherapy regularly during their in-patient stay.

Our study had several strengths. It was one of the largest randomized controlled trials in the field of allo-HCT. Due to our large sample size, it was possible to perform a subgroup analysis, investigating training response in initially *fit* and *unfit* patients. To our knowledge, no study has examined whether cancer patients with different initial fitness levels respond differently on physical exercise training; this question is essential and should be addressed when prescribing or designing exercise programs in the future. Moreover, our intervention was treatment setting overlapping, starting 1–4 weeks before admission and ending 6–8 weeks after discharge, and, our exercise training was only partly supervised, and can therefore be easily adapted into clinical practice.

Our study also has some limitations. First, this is a retrospective subgroup analysis of an exercise intervention trial. Thus, the baseline characteristics concerning physical fitness were not randomly allocated. Another limitation was that age- and gender-specific norm values were not available for all measured muscle groups, thus we were unable to perform our analyses with all measured muscle groups. Nevertheless, based on the observed results, we expect comparable developments in the other muscle groups.

The clinical implications of our results emphasize the importance of exercise training in initially *unfit* patients during and after allo-HCT. Oncologists and exercise therapists should consider that it is possible to perform exercise in *unfit* patients as well as in *fit*

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patients, which might be very important with regard to recommended preventive practices in HCT patients[28] or new findings in the area of hematological reconstitution after HCT.[29] Our findings also suggest that initially *fit* patients may require more intense exercise recommendations to achieve similar benefits to *unfit* patients. Furthermore, it is essential to communicate and interpret the potential fitness losses that may occur in initially *fit* patients appropriately.

Future research should focus on similar investigations in other cancer entities and examine which subgroups might benefit more from exercise during and after cancer treatment as well as try to answer the question regarding optimal standards (frequency, intensity and time) of exercise in those subgroups. Furthermore, it might be very important in future studies to link physical activity behavior with the nutritional status of HCT patients[30,31] to obtain more insight into the relation between those two aspects. With regard to methodological aspects, our results also emphasize that baseline fitness levels should be considered as a stratifying criterion in randomization procedures to preclude a fitness bias in statistical analyses of clinical exercise trials.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

The study was funded by the German Jose Carreras Leukemia Foundation (2006–2008; project no. R05/33p).

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