Impact of HSCT conditioning and glucocorticoid dose on exercise adherence and response

Medicine & Science IN Sports & Exercise
The Official Journal of the American College of Sports Medicine
www.acsm-msse.org

. . . Published ahead of Print

Impact of HSCT Conditioning and Glucocorticoid Dose on Exercise Adherence and Response

Joachim Wiskemann[1], Benedikt Herzog[1], Rea Kuehl[1], Martina E.Schmidt[2], Karen Steindorf[2], Rainer Schwerdtfeger[6], Peter Dreger[3], and Martin Bohus[4,5]

[1]Department of Medical Oncology, National Center for Tumor Diseases (NCT) and Heidelberg University Hospital, Germany; [2]Division of Physical Activity, Prevention and Cancer, National Center for Tumor Diseases (NCT) and German Cancer Research Center (DKFZ), Heidelberg, Germany; [3]Department of Medicine V, Heidelberg University Hospital, Heidelberg, Germany; [4]Central Institute of Mental Health, Mannheim, Germany; [5]Faculty of Health, University of Antwerp, Belgium; [6]Bone Marrow Transplant Unit, German Clinic for Diagnostics, Wiesbaden, Germany

Accepted for Publication: 12 June 2017

Medicine & Science in Sports & Exercise, Publish Ahead of Print
DOI: 10.1249/MSS.0000000000001357

Impact of HSCT Conditioning and Glucocorticoid Dose on Exercise Adherence and Response

Joachim Wiskemann[1], Benedikt Herzog[1], Rea Kuehl[1], Martina E.Schmidt[2], Karen Steindorf[2], Rainer Schwerdtfeger[6], Peter Dreger[3], and Martin Bohus[4,5]

[1]Department of Medical Oncology, National Center for Tumor Diseases (NCT) and Heidelberg University Hospital, Germany; [2]Division of Physical Activity, Prevention and Cancer, National Center for Tumor Diseases (NCT) and German Cancer Research Center (DKFZ), Heidelberg, Germany; [3]Department of Medicine V, Heidelberg University Hospital, Heidelberg, Germany; [4]Central Institute of Mental Health, Mannheim, Germany; [5]Faculty of Health, University of Antwerp, Belgium; [6]Bone Marrow Transplant Unit, German Clinic for Diagnostics, Wiesbaden, Germany

Corresponding author:

Joachim Wiskemann (PhD)

National Center for Tumor Diseases (NCT)

Division of Medical Oncology

Im Neuenheimer Feld 460

69120 Heidelberg, Germany

Phone: +49 (0)6221 / 56 - 5904

E-Mail: joachim.wiskemann@nct-heidelberg.de

Disclosure of Funding:

This work was supported by the Deutsche José Carreras Leukämie Stiftung e.V. (project no. R05/33p; R10/42pf and R13/27)). Dr. Wiskemann was supported by the "Manfred-Lautenschlaeger-Stiftung".

Conflict of interest disclosure:

The authors disclose professional relationships with companies or manufacturers who will benefit from the results of the present case study. The results of the present case study do not constitute endorsement by ACSM.

ABSTRACT

Purpose: Evidence from randomized controlled trials (RCT) is growing that exercise interventions have beneficial effects in patients undergoing allogeneic stem cell transplantation (allo-HSCT). However, intensive chemotherapy conditioning as well as glucocorticoid (GC) treatment is always part of an allo-HSCT and possibly impact exercise adherence and training response. Therefore, we aimed to examine whether various conditioning protocols or different doses of GC treatment affect exercise adherence and/or training response during the inpatient period.

Methods: We analyzed inpatient data from intervention groups of two large RCTs in allo-HSCT patients (n=113). The intervention incorporated partly supervised endurance and resistance exercise 3-5x/week. According to the potentially interfering factors patients were divided into groups depending on intensity of conditioning (myeloablative conditioning (MAC), reduced-intensity conditioning (RIC) and nonmyeloablative conditioning (NMC)) and cumulative dose of GC treatment (GC LOW ≤ 9 mg/kg prednisone or GC HIGH > 9 mg/kg prednisone) and were compared.

Results: Median exercise adherence (target value 5 sessions weekly) during the inpatient period was 64% in MAC, 54% in RIC and 63% in NMC. The proportion of prematurely terminated training sessions ranged from 11% to 15%. Tiredness was the most frequent cause of exercise termination in all groups. Exercise adherence, duration (minutes/week) and type of training was

significantly associated with GC dose. With regard to training response, results suggest GC LOW patients tend to respond better in knee extensor muscle strength.

Conclusions: Exercise adherence during inpatient period is significantly impacted by dose of GC treatment but not by condition regimen. However, given the reasonable adherence rates also in the GC HIGH group data supports the feasibility and importance of exercising for all allo-HSCT patients during the inpatient period.

Keywords: physical activity, cancer, treatment protocol, allogeneic, transplantation, oncology

INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is an intense medical treatment with curative intention for patients with high-risk hematological malignancies such as leukemia or lymphoma. Over the past decade there has been a growing body of evidence suggesting that exercise interventions have beneficial effects in patients treated with allo-HSCT e.g. reducing side effects such as fatigue, maintaining physical function during treatment and beyond and improving global quality of life (24). Meanwhile, general exercise recommendations for cancer patients (27), even in the specific field of allo-HSCT (29) have been published. After our group was able to demonstrate the general effectiveness of exercise intervention on physical performance and psychosocial well-being (28) in 105 allo-HSCT patients, we examined whether the individual training response depends on the initial performance level. We demonstrated that training response was superior in unfit patients compared to fit patients which is of high clinical relevance, because in clinical practice exercise is often not recommended especially for patients with poor health status (32).

However, components of the allo-HSCT treatment regimens may adversely affect the success of an exercise-based rehabilitation. One potentially influencing aspect might be the conditioning regimen prior to transplantation, which consists of chemotherapy alone or a combination of chemotherapy and radiotherapy (1). Various conditioning regimens are currently existing ranging from high toxicity, myeloablative conditioning, which is often limited to younger patients without comorbidities, to reduced intensity conditioning regimens to make allo-HSCT also accessible for patients of advanced age or with comorbidities (3). Another possible interfering aspect with regard to exercise-based rehabilitation might be the dosing of

glucocorticoids (GC). GC represents an optimal treatment of graft-versus-host disease (GvHD) which is a frequent and potentially life-threatening complication of allo-HSCT (4). However, GC therapy is well-recognized for causing significant adverse effects such as muscle loss, reduced muscle function, physical performance deficits, hyperglycemia, increased risk of infection, mood changes and weight gain (14, 23).

Based on the current knowledge and given the challenging situation of intense treatment modalities, we here aimed to investigate whether various conditioning protocols and/or different doses of GC treatment alter exercise adherence and training response during inpatient allo-HSCT. Therefore, we analyzed inpatient data from two large RCTs in patients undergoing allo-HSCT.

METHODS

Design and participants

The manuscript follows the STROBE Statement for report of cohort studies. Data were obtained from the experimental groups (EG) of two RCTs in allo-HSCT patients. Forty patients were recruited as part of the study published in the journal *blood 2011* (28) (BLOOD study). The BLOOD study was a prospective, multicenter, clinical RCT in cancer patients, before, during and after allo-HSCT, comparing a self-administered exercise intervention with a social contact control group. Further 73 patients were recruited as part of the study "Physical Exercise Training versus Relaxation in Allogeneic stem cell transplantation" (PETRA study). The PETRA study is a large, still on-going RCT in cancer patients during and after allo-HSCT. Primary outcome is 2-year overall survival since we found positive effects of exercise on survival in a post-hoc

analysis of the BLOOD study (30). The study designs have been reported elsewhere (28, 31) and the local ethic committees approved the studies. Inclusion criteria were scheduled for allo-HSCT at the Heidelberg University Clinic (both studies) or the German Clinic for Diagnostic Wiesbaden (only BLOOD study), age ≥18 years and the ability to understand and follow the study protocol. Exclusion criteria were inability to walk or stand, instable bone lesions, severe neurological deficiencies, severe cardiac or cardiovascular diseases, and/or severe pulmonary global insufficiency. The PETRA study is registered at ClinicalTrials.gov (NCT01374399). In both studies written informed consent was obtained from each participant prior first assessment. A both study integrating patient flow diagram is presented in supplementary figure 1 (see Figure, Supplemental Digital Content 1, Patient Flow of the BLOOD and PETRA-Study, http://links.lww.com/MSS/A976).

Analyses presented here included data only from patients of the EG, which could be tested on assessment points time of admission to the hospital and time of discharge. Data from the PETRA and the BLOOD study was used for training response analyses with regard to conditioning regimens, whereas only data from the PETRA study was used for exercise adherence and GC treatment analyses.

Intervention

The exercise prescription of both studies was identical with regard to the analyzed inpatient period. Patients assigned to the EG started the partly supervised inpatient intervention program (endurance and resistance exercise, 3-5x/week) at the first day in isolation units at the hospital. Two to three exercise sessions per week were supervised. Exercise intensity was individually

adapted. Further details are prescribed in our previous publications (28, 31). Patients were informed about contraindications for exercise sessions such as thrombocytopenia, infections, fever, strong pain and dizziness.

Measurements

Assessment points were prior allo-HSCT and at the day of discharge. Physical performance was assessed with the 6-minute walk test (6MWT) (9) and isometric muscle strength of various muscle groups was measured by hand-held dynamometry (HHD) (6). Within the 6MWT patients were advised to walk back and forth down a hallway as fast as possible for six minutes. The six-minute walk distance was assessed in meters. Heart rate and oxygen saturation was measured before, during and after the test. Isometric muscle strength was assessed for knee extensors and flexors (both in seated position with 90° angle of knee flexion), elbow extensor and flexors as well as for hip flexors (all in recumbent position). Three attempts were performed in each muscle group. The mean value was used for further calculations. In case of a deviation of ≥30% of the corresponding median, mean was calculated of the two best values. To assess exercise adherence, patients documented each training day in standardized exercise logs. Total exercise duration per day (minutes), the type of exercise performed (resistance, endurance, or a combination of both) and reasons for prematurely terminating a training session was recorded.

Classification of the study population based on the intensity of conditioning

In order to allow comparisons between studies and interpretation of study results, Bacigalupo et al. proposed to standardize the classification of conditioning regimens by building three categories: myeloablative conditioning (MAC), reduced-intensity conditioning (RIC), and

nonmyeloablative conditioning (NMC), based on duration of pancytopenia and requirement for stem cell support (2). In contrast to RIC and NMC there is a strong antitumor effect in MAC. However, all types of conditionings have an intense immunosuppressive effect. Due to high toxicity, MAC is only applied in young (max. 50 years) and fit patients without severe comorbidity, whereas RIC and NMC is also administered to older and unfit patients.

Glucocorticoid dose

To investigate the impact of glucocorticoid (GC) treatment on exercise adherence and training response all GC containing drugs were converted into the potency of prednisone and a cumulative dose of prednisone was calculated for each individual. Then patients were divided in two groups (GC LOW≤ 9 mg/kg prednisone and GC HIGH> 9 mg/kg prednisone), depending on the cumulative dose of GC treatment they received. The cut-point of 9 mg/kg was chosen from the median of all values.

Statistical analysis

Baseline and other group characteristics were compared across the three conditioning groups using analysis of variance, Kruskal-Wallis test, or Fisher's exact test. Training frequency was calculated for the inpatient period as number of sessions divided by the individual period length (in weeks), i.e. number of completed sessions/week. Exercise duration was calculated as total minutes of exercise during the inpatient period divided by the period length (in weeks), i.e. min/week. As the intervention guidelines require three to five completed training sessions weekly, exercise adherence was calculated as the frequency of completed training sessions/week divided by 3 times*100, with three or more sessions set to 100% adherence. Similarly, exercise

adherence based on a target value of five completed sessions per week was calculated. Regarding training response, we calculated the absolute and the percentage change from time of admission to hospital to time of discharge for MAC, RIC and NMC. For 3-group comparison (MAC, RIC and NMC), we conducted an analysis of covariance (ANCOVA) controlling for age, gender and the baseline value of the response variable. We explored also other potential confounders like hemoglobin or self-reported exercise behavior prior to allo-HSCT without showing significant differences in the results. For analyzing the impact of GC therapy on exercise adherence and training response, the study population was divided into two groups using the median as cutpoint ($\leq$ 9 mg/kg prednisone and > 9 mg/kg prednisone). All statistical analyses were performed with SAS Version 9.3 with significance level set at $\alpha = 0.05$.

RESULTS

Recruitment and retention

Recruitment of the BLOOD study took place from May 2007 until September 2008 and n=40 patients were randomized in the EG at the day of admission. Recruitment of PETRA patients for this analysis took place from February 2011 until October 2013. At the day of admission 73 patients were randomized in the EG (see Figure, Supplemental Digital Content 1, Patient Flow of the BLOOD and PETRA-Study, http://links.lww.com/MSS/A976). Demographic and medical characteristics of the study participants are described in Table 1. Patient characteristics grouped by MAC, RIC and NMC showed significant differences in age (P<.01) and hemoglobin levels (P=.017).

➔ Table 1: Baseline characteristic of the study population

Applied conditioning regimens

Classification of the study population depending on the conditioning regimen is shown in Table 2. Due to readability some conditioning regimens were summarized.

➔ Table 2: Classification of conditioning

Exercise Adherence

Exercise adherence data depending on the conditioning regime is shown in table 3, based on the returned logs. Unfortunately, due to the proportion of missing exercise logs in the BLOOD-Study (24% in the inpatient period), we decided to exclude all BLOOD-Study patients from our exercise adherence analysis. Median adherence to the exercise intervention (target value 3 sessions/ target value 5 sessions) was comparable between groups (see table 3). Exercise duration reached the highest amount in NMC but differences were not significant. There were no differences in proportion of prematurely terminated training sessions either. The most frequent cause of premature termination of training sessions was fatigue in all three groups, similarly followed by nausea and pain.

➔ Table 3: Impact of conditioning on exercise adherence

Table 4 presents exercise adherence data depending on GC treatment. Median adherences to the exercise intervention were predominantly in favor for GC LOW in comparison to GC HIGH group. GC LOW showed a longer exercise duration compared to GC HIGH (92.4 vs. 71.1

min/week, P = .01) as well as a higher exercise frequency (3.8 vs. 3.2 sessions/week, P = .02). The main difference with regard to type of exercise were observed in frequency of strength training sessions (1.5 vs. 1.1 sessions/week, P = .02). There was also an advantage for GC LOW regarding percentage of incomplete sessions, however, without reaching statistical significance.

➔ Table 4: Impact of GC treatment on exercise adherence

Training response

Training response data for MAC, RIC and NMC are presented in table 5. Both, strength and endurance values decreased across all three groups during the inpatient period. The only exception represented hip-flexion of NMC which increased in this group by about 5% during the inpatient period. Group comparison revealed no significant difference.

➔ Table 5: Impact of conditioning regime on training response

Table 6 presents training response depending on the glucocorticoid dose. The strength decline tended to be lower in GC LOW compared to GC HIGH for knee extension. However, other parameters seem to be unaffected. When adjusting for exercise adherence using exercise duration as adherence variable the results did not change (data not shown). Interestingly, strength values as well as 6MWT distance were higher in the GC LOW group at baseline.

➔ Table 6: Impact of GC treatment on training response

DISCUSSION

Within this study we were examining the impact of various conditioning regimens and different doses of glucocorticoid (GC) treatment on exercise adherence and training response during the inpatient treatment period of allo-HSCT patients. We observed that exercise adherence (frequency and duration) was significant higher in the GC LOW group and therefore related to dose of GC treatment. However, adherence was not significantly affected by the conditioning regimen. The percentage of incomplete sessions showed no significant difference, neither for conditioning groups nor for GC groups and fatigue was the most frequent cause of exercise termination in all groups. With regard to training response, results showed a trend that GC LOW declined less in knee extensor muscle strength than GC HIGH, whereas in relation to the conditioning regimen no association could be observed. As expected, most training response parameters declined during the inpatient treatment period.

Exercise adherence is the extent to which a person fulfills the prescribed study protocol (33). Recently, our group published an analysis of adherence data in allo-HSCT patients during and after treatment (17), here we further refine our results when comparing different conditioning regimens and GC doses. In our current analyses median exercise frequency (target value 3 sessions weekly) to inpatient exercise in all conditioning groups was above 90%. Even with regard to a target frequency of 5 sessions weekly, median exercise adherence was still high with 64% in MAC, 54% in RIC and 63% in NMC. Median exercise duration (including complete and incomplete sessions) was 71 min/week in MAC, 84 min/week in RIC and 100 min/week in NMC. Meaning, that median exercise duration decreased with increasing intensity of conditioning, however, without reaching significance level. One possible explanation for this

finding might be that patients with more intense conditioning experienced more negative side-effects, resulting in less exercise participation. Our result that the MAC group had the highest percentage of incomplete sessions underlines this consideration. Most frequent reason for exercise termination was fatigue, indicating that fatigue is a challenging factor when performing exercise in this patient group. This was already shown before (17).

Regarding exercise frequency between GC LOW and GC HIGH, differences in favor for the GC LOW patients were observed. GC LOW patients performed significant more training sessions per week than GC HIGH patients. Furthermore, exercise duration was significant longer in GC LOW patients (92 min/week) than in GC HIGH patients (71 min/week). Related to the type of exercise, GC LOW patients were significantly more engaged in resistance training than GC HIGH patients. However, this does not result in significantly different training adaptations even if knee extensor strength develops a little bit better during the intervention period. This is an interesting finding because we would have expected that GC LOW patients respond better, particularly when performing a greater volume (frequency and duration) of exercise. One possible explanation for this discrepancy is that the exercise performed was not intense enough since exercise intensity is known as the most important component for training adaptions (12). Unfortunately, we did not record achieved exercise intensity within our training logs.

A recent review pointed out that the majority of all supervised studies in the transplant setting did not report exercise adherence data (13). In the context of allo-HSCT only two other groups were reporting on adherence to exercise protocol. The study by Jarden et al. reported 90% (67-100%) average adherence (defined as attendance) to a 5x/week supervised multimodal exercise

program during the inpatient period for allo-HSCT (4-6 weeks) (15). Although being a supervised intervention program, patients participated more in resistance training (98% of sessions were performed) than in endurance exercise sessions (on average, 80% (60-96%) of sessions were performed). This is consistent with our results. Another study done by DeFor et al. reported that 10 of 42 patients (24%) were able to perform a 30-minute daily, unsupervised walking intervention during and after allo-HSCT (10). Respectively, 76% were not able to perform 30 minutes of daily walking during the whole intervention period. Unfortunately, an average adherence rate of the whole study population was not reported. However, none of the above mentioned studies reported adherence rates in relation to the applied condition regimens or GC treatment.

Only one retrospective study by Morris et al. (22) examined exercise adherence data in the context of GC treatment during the early rehabilitation period. The overall adherence was 61% in a 4-week outpatient progressive exercise rehabilitation program. Additionally, they showed that 54% of the 59 observed GC-treated allo-HSCT patients were able to complete at least 80% of the prescribed exercise sessions. Given the situation, that exercise was prescribed individually between 2-3x/week for 30-45 minutes it could be suggested that our adherence rates were higher; however, the comparability of the studies is limited due to different time periods observed and the individual exercise prescription by Morris et al. A further limitation is given by the fact the only the absolute and not the relative dose of GC treatment was reported. Comparable to our results, in patients that adhered to the exercise program there were no difference in the adherence rate between patients received myeloablative or low dose conditioning prior transplantation. However, there were numerically more patients receiving low-dose conditioning in the non-

adherent group by Morris et al. Further, in terms of GC treatment, the study by Morris et al. could not find differences in adherence data (22). This is in contrast with our result where GC LOW patients exercised significant more than the GC HIGH patients. Moreover, in another publication the authors report on adherence data in a comparable patient group of allo-HSCT patients without GC treatment. In this group, the adherence was lower, but no exact numbers were reported (21, 22). Regarding training response, the comparison of both studies by Morris et al. indicated a slightly better response in non-GC treated patients, however, no direct comparison between studies was performed (22). Nevertheless, these results support our tentative findings, that GC LOW patients might have a better training response.

Recent studies reported that an exercise intervention under allo-HSCT does not result in an increase, but can prevent the loss of physical performance compared to a control group (5, 15, 28). Based on our data reported here we can confirm these findings but we were also able to provide a more detailed insight on this perspective by showing that the loss of physical performance in exercising patients was not significantly affected by the conditioning regime or GC dose. With exception of the NMC group in hip flexion patients were unable to increase physical performance during the inpatient setting in allo-HSCT. An increment in strength and endurance performance seems to be achievable only during the outpatient setting immediately after allo-HSCT (16, 28).

Besides it positive effects (18), it is known that GC treatment has a catabolic effect on skeletal muscles by increased protein breakdown and decreased protein synthesis which is caused by the stimulation of the ubiquitin-proteasome proteolytic pathway (25) as well as the lysosomal system

(26). Several genes are discussed to be involved in the proteolytic process as mediators like FOXO, Antrogin-1 or MuRF-1. The inhibition of muscle protein synthesis can be mainly explained by the GC mediated inhibition of the mTOR/S6 kinase 1 pathway (26). Lower limb skeletal muscle groups seems to be more affected than upper limb groups (19). This is also supported by findings of a previous observational study among 113 allo-HSCT patients where the authors report a significant association between total GC dose and decrease of knee extensors strength during inpatient treatment (20). Even the reduction in muscle strength found in our study is probably caused by GC treatment. However, it remains uncertain whether exercise has the capability to counteract GC-induced myopathy. As mentioned above, our data indicated that there were no significant differences in training response leading to the assumption that exercise might attenuate side-effects of higher doses of GC treatment. Given the fact that even increments in physical performance could be achieved in pediatric cancer patients during the transplantation period (7), it would be of interested to focus also on this population with regard to a potential modification through GC treatment. Also having in mind the shown positive effects on the immune system in this population (7, 8) and the potentially GvHD modulation by structured exercise programs (11).

Our study had several strengths. Due to the large sample size, it was possible to perform subgroup analyses, investigating exercise adherence and training response in patients with different conditioning intensities. To our knowledge, no prospective study has examined whether cancer patients with different conditioning intensities adhere and/or respond differently to physical exercise training during the inpatient period of allo-HSCT treatment. Furthermore, we performed the same analyses with regard to GC treatment which is also unique in this patient

population. Both aspects are essential and should be considered when designing, prescribing and evaluating exercise interventions in the future.

Our study has also limitations. Firstly, even the overall sample size was quite large for an allo-HSCT study, the numbers in the considered subgroups were in part small, hence might have hindered to detect significant group differences with regard to mentioned parameters. It also should be noted that analyses were explorative in nature and therefore no adjustments for multiple testing were performed. Secondly, the working definitions from Bacigalupo et al. for conditioning classification should be regarded as a first reference point, which might need to be discussed and adapted in the future. Some classification criteria are debated controversial and some definitions are partly based on consensus decisions only (3). Thirdly, the comparability of the studies included is partly limited since the BLOOD study had a preceding outpatient home-based training period prior to allo-HSCT which might have led to first training adaptions before admission to hospital resulting in turn in less adaption effects during the inpatient period. However, previously published data suggests that patients were not able to increase physical performance during this short (mean 21 days) pre-hospital intervention period (28).

In conclusion, our study demonstrates that a partly supervised exercise intervention program is feasible and well accepted during allo-HSCT treatment and is not significantly affected by applied conditioning regimes. However, our findings revealed that receiving GC treatment in higher doses negatively impacts training frequency and duration but exercising remains possible. Nevertheless, these lower adherence values do not result in significant reduced physical performance scores. These findings should encourage physicians and exercise

specialist/physiotherapists to promote and provide exercise for all patients undergoing allo-HSCT bearing in mind that differential adherence rates related to GC treatment are possible. Due to the variability in the observed data, more research is needed to further evaluate optimal exercise prescriptions regarding various treatment conditions and to improve training adherence and response, predominantly in patients affected by high-dose GC treatment.

ACKNOWLEDGEMENTS

We would like to thank the patients who participated in this clinical trial. We also thank the Institute of Sports and Sports Science of the University of Heidelberg for providing the training facilities; Matthias Limbach, Tamara Christ, Lena Kempf, Marcel Bannasch, and Beate Biazeck for partly performing the interventions; Herrad Baurmann, MD, Thomas Luft, MD, Birgit Friedmann-Bette, MD, Andrea Bondong and Angelika Cook for medical support and/or help with recruitment; Petra Armbrust, for study assistance; and Werner Diehl, PhD, for data management.

The results of the study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation.

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interests: The Authors declare no conflict of interests.

Informed consent: Informed consent was obtained from all individual participants included in the study. This process was supervised by the local ethics committee.

DISCLOSURE OF FUNDING

This work was supported by the Deutsche José Carreras Leukämie Stiftung e.V. (project no. R05/33p; R10/42pf and R13/27)). Dr. Wiskemann was supported by the "Manfred-Lautenschlaeger-Stiftung".

REFERENCES

1. Arnold ME, Taylor NF. Exercise for patients with cancer: reducing disease-related fatigue. *Future Oncol*. 2011;7(2):165-7.
2. Bacigalupo A, Ballen K, Rizzo D et al. Defining the intensity of conditioning regimens: working definitions. *Biol Blood Marrow Transplant*. 2009;15(12):1628-33.
3. Barrett AJ, Savani BN. Stem cell transplantation with reduced-intensity conditioning regimens: a review of ten years experience with new transplant concepts and new therapeutic agents. *Leukemia*. 2006;20(10):1661-72.
4. Barton-Burke M, Dwinell DM, Kafkas L et al. Graft-versus-host disease: a complex long-term side effect of hematopoietic stem cell transplant. *Oncology (Williston Park)*. 2008;22(11 Suppl Nurse Ed):31-45.
5. Baumann FT, Zopf EM, Nykamp E et al. Physical activity for patients undergoing an allogeneic hematopoietic stem cell transplantation: benefits of a moderate exercise intervention. *Eur J Haematol*. 2011;87(2):148-56.
6. Bohannon RW. Reference values for extremity muscle strength obtained by hand-held dynamometry from adults aged 20 to 79 years. *Arch Phys Med Rehabil*. 1997;78(1):26-32.
7. Chamorro-Vina C, Ruiz JR, Santana-Sosa E et al. Exercise during hematopoietic stem cell transplant hospitalization in children. *Med Sci Sports Exerc*. 2010;42(6):1045-53.
8. Chamorro-Vina C, Valentin J, Fernandez L et al. Influence of a Moderate-Intensity Exercise Program on Early NK Cell Immune Recovery in Pediatric Patients After Reduced-Intensity Hematopoietic Stem Cell Transplantation. *Integrative cancer therapies*. epub Nov 2016.

9. Crapo R, Casaburi R, Coaties A et al. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med*. 2002;166(1):111-7.

10. DeFor T, Burns L, Gold E, Weisdorf D. A Randomized Trial of the Effekt of a Walking Regimen on the Functional Status of 100 Adult Allogeneic Donor Hematopoietic Cell Transplant Patients. *Biology of Blood and Marroww Transplantation*. 2007;13:948-55.

11. Fiuza-Luces C, Garatachea N, Simpson RJ, Berger NA, Ramirez M, Lucia A. Understanding graft-versus-host disease. Preliminary findings regarding the effects of exercise in affected patients. *Exerc Immunol Rev*. 2015;21:80-112.

12. Garber CE, Blissmer B, Deschenes MR et al. American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. *Med Sci Sports Exerc*. 2011;43(7):1334-59.

13. Hacker ED, Mjukian M. Review of attrition and adherence in exercise studies following hematopoietic stem cell transplantation. *Eur J Oncol Nurs*. 2014;18(2):175-82.

14. Herold G. Glukokortikosteroide. In: Herold, G. und Mitarbeiter. Innere Medizin. 2013:781-3.

15. Jarden M, Baadsgaard MT, Hovgaard DJ, Boesen E, Adamsen L. A randomized trial on the effect of a multimodal intervention on physical capacity, functional performance and quality of life in adult patients undergoing allogeneic SCT. *Bone Marrow Transplant*. 2009;43(9):725-37.

16. Knols RH, de Bruin ED, Uebelhart D et al. Effects of an outpatient physical exercise program on hematopoietic stem-cell transplantation recipients: a randomized clinical trial. *Bone Marrow Transplant*. 2011;46(9):1245-55.

17. Kuehl R, Schmidt ME, Dreger P, Steindorf K, Bohus M, Wiskemann J. Determinants of exercise adherence and contamination in a randomized controlled trial in cancer patients during and after allogeneic HCT. *Support Care Cancer*. 2016;24(10):4327-37.

18. Lin KT, Wang LH. New dimension of glucocorticoids in cancer treatment. *Steroids*. 2016;111:84-8.

19. Minetto MA, Lanfranco F, Motta G, Allasia S, Arvat E, D'Antona G. Steroid myopathy: some unresolved issues. *Journal of endocrinological investigation*. 2011;34(5):370-5.

20. Morishita S, Kaida K, Yamauchi S et al. Relationship between corticosteroid dose and declines in physical function among allogeneic hematopoietic stem cell transplantation patients. *Support Care Cancer*. 2013;21(8):2161-9.

21. Morris GS, Brueilly KE, Scheetz JS, Brannan EA. Functional performance status of hematopoietic SCT recipients in the sub-acute phase of recovery. *Bone Marrow Transplant*. 2010;45(4):755-61.

22. Morris GS, Brueilly KE, Scheetz JS, de Lima MJ. Adherence of stem cell transplant recipients receiving glucocorticoid therapy to an exercise-based rehabilitation program. *Support Care Cancer*. 2012;20(10):2391-8.

23. Oray M, Abu Samra K, Ebrahimiadib N, Meese H, Foster CS. Long-term side effects of glucocorticoids. *Expert Opin Drug Saf*. 2016;15(4):457-65.

24. Persoon S, Kersten MJ, van der Weiden K et al. Effects of exercise in patients treated with stem cell transplantation for a hematologic malignancy: a systematic review and meta-analysis. *Cancer treatment reviews*. 2013;39(6):682-90.

25. Price SR, Du JD, Bailey JL, Mitch WE. Molecular mechanisms regulating protein turnover in muscle. *Am J Kidney Dis*. 2001;37(1 Suppl 2):S112-4.

26. Schakman O, Kalista S, Barbe C, Loumaye A, Thissen JP. Glucocorticoid-induced skeletal muscle atrophy. *Int J Biochem Cell Biol*. 2013;45(10):2163-72.

27. Schmitz KH, Courneya KS, Matthews C et al. American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. *Med Sci Sports Exerc*. 2010;42(7):1409-26.

28. Wiskemann J, Dreger P, Schwerdtfeger R et al. Effects of a partly self-administered exercise program before, during, and after allogeneic stem cell transplantation. *Blood*. 2011;117(9):2604-13.

29. Wiskemann J, Huber G. Physical exercise as adjuvant therapy for patients undergoing hematopoietic stem cell transplantation. *Bone Marrow Transplant*. 2008;41(4):321-9.

30. Wiskemann J, Kleindienst N, Kuehl R, Dreger P, Schwerdtfeger R, Bohus M. Effects of physical exercise on survival after allogeneic stem cell transplantation. *Int J Cancer*. 2015;137(11):2749-56.

31. Wiskemann J, Kuehl R, Dreger P et al. Physical Exercise Training versus Relaxation in Allogeneic stem cell transplantation (PETRA Study) - Rationale and design of a randomized trial to evaluate a yearlong exercise intervention on overall survival and side-effects after allogeneic stem cell transplantation. *BMC Cancer*. 2015;15(1):619.

32. Wiskemann J, Kuehl R, Dreger P et al. Efficacy of exercise training in SCT patients--who benefits most? *Bone Marrow Transplant*. 2014;49(3):443-8.

33. World Health Organisation (WHO). Adherence to Long-term Therapies: Evidence for Action. In: WHO Library Cataloguing-in-Publication Data, Switzerland; 2003.

FIGURE LEGENDS

Supplementary Figure 1: Patient Flow of the BLOOD and PETRA-Study.

Supplementary Figure 1

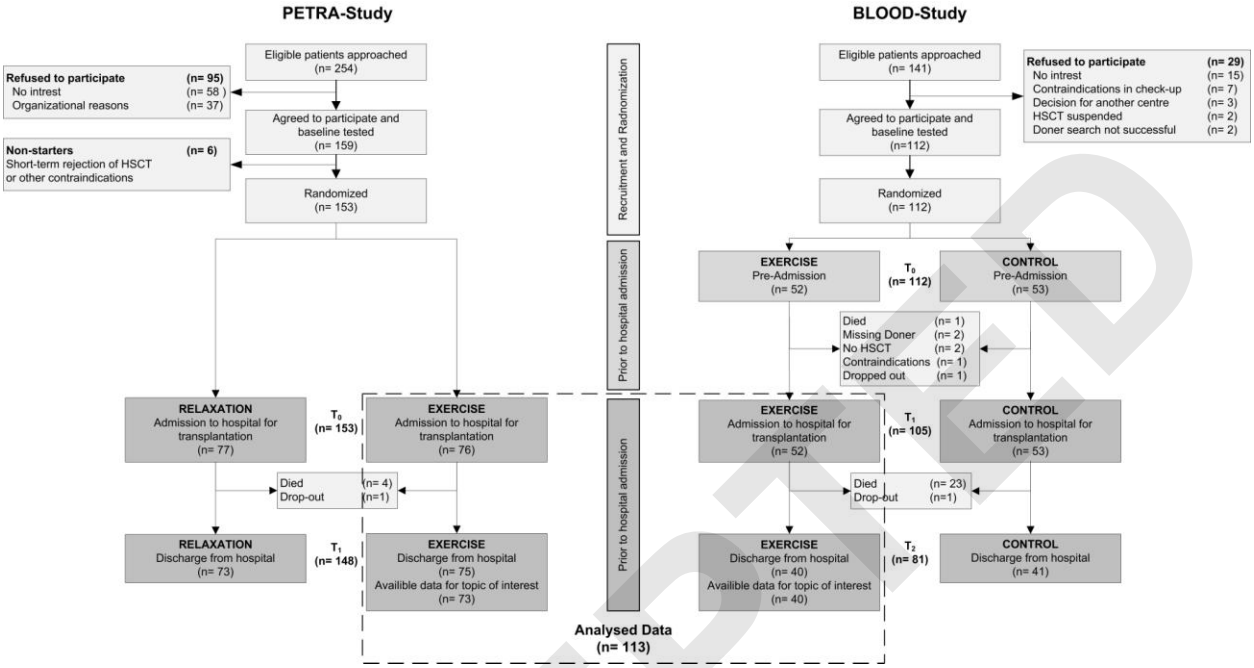

Table 1: Baseline characteristics of the study population

	All (*n* = 113)	MAC (*n* = 39)	RIC (*n* = 64)	NMC (*n* = 10)	*P**
Study					0.34
BLOOD	40 (35%)	17 (44%)	21 (33%)	2 (20%)	
PETRA	73 (65%)	22 (56%)	43 (67%)	8 (80%)	
Age (yr)	51 ± 13	45 ± 15	55 ± 10	52 ± 6	<0.01
Sex					
Male	74 (64%)	24 (62%)	44 (69%)	6 (60%)	0.72
Female	39 (35%)	15 (38%)	20 (31%)	4 (40%)	
BMI (kg/m^2)	26.6 (4.5)	27.6 (5.9)	26.0 (4.1)	26.7 (2.2)	0.42
Hemoglobin level (g/dl)	11.2 (1.9)	10.9 (1.9)	11.2 (1.8)	13.0 (1.9)	<0.02
Diagnosis					
ALL	8	7	1	0	
AML	33	6	27	0	
CLL	18	4	10	4	
CML	2	1	0	1	
M. Hodgkin	3	0	3	0	
MDS (incl. CMML)	13	3	10	0	
Multiple Myeloma	12	5	6	1	
MPS	2	2	0	0	
NHL	14	7	5	2	
CIMF	5	3	2	0	
AL-Amyloidose	1	0	0	1	
Aplastic anemia	1	1	0	0	
Pancreas carcinoma	1	0	0	1	
Source of stem cell					0.48
Peripheral blood cells	104	34	60	10	
Bone marrow	7	4	3	0	
Donor-recipient characteristics					0.20
Related	28	9	14	5	
Unrelated	83	29	49	5	

Abbreviations: BMI, body mass index; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; MDS, myelodysplastic syndrome; CMML, chronic myelomonocytic leukemia; MPS, myeloproliferative syndrome; NHL, non-Hodgkin lymphoma; CIMF, chronic idiopathic myelofibrosis

*ANOVA or Fisher's exact test, respectively.

Values are presented as mean ± SD or absolute and relative frequencies.

Table 2: Classification of conditioning

	MAC (*n* = 39)	RIC (*n* = 64)	NMC (*n* = 10)
Conditioning regimens			
TBI 12 Gy + Eto 60mg/kg	2		
TBI 8-12 Gy + Cyc 80-240 mg/kg ± Flu 120 mg/kg	15		
TBI 8 Gy + Flu 120 mg/m²	13		
TBI 8 Gy + Thio 10 mg/kg + Flu 150 mg/m²	1		
TBI 6 Gy + Flu 90-120 mg/m²		5	
TBI 4 Gy + Flu 120 mg/m² + Cyc 80 mg/kg		1	
TBI 2 Gy + Flu 90 mg/m²			3
Bu 4-8 mg/kg p.o. + Flu 125-150 mg/m²		8	
Bu 10-15 mg/kg p.o. + Flu 125-180 mg/m²	5		
Bu 12-16 mg/kg p.o.+ Cyc 120-160 mg/kg	3		
Flu 150 mg/m² + Cyc 3.750 mg/kg			7
Treo 30-42 g/m² + Flu 150 mg/m²		19	
FLAMSA		17	
Mel 140-150 mg/m² + Flu 90-150 mg/m²		14	

Abbreviations: TBI, total body irradiation; Eto, etoposide; Cyc, cyclophosphamide; Flu, fludarabine; Thio, thiotepa; Treo, treosulfan, FLAMSA, fludarabin Ara-C amsacrin, Mel, melphalan

Table 3: Impact of conditioning on exercise adherence

Variable	MAC (*n* = 22)	RIC (*n* = 43)	NMC (*n* = 8)	*P*
Adherence to protocol (%) Reference value 3 sessions weekly	100.0 (77.8, 100.0)	90.3 (66.0, 100.0)	100.0 (78.0, 100.0)	0.26
Adherence to protocol (%) Reference value 5 sessions weekly	64.1 (46.7, 73.9)	54.2 (39.6, 70.0)	63.2 (46.8, 80.9)	0.36
Exercise duration (min/week)	71.1 (57.5, 111.0)	83.5 (51.2, 108.0)	100.4 (81.7, 118.9)	0.38
Training frequencies (sessions/week)				
Total	3.4 (3.0, 4.3)	3.4 (2.2, 4.1)	4.1 (3.4, 4.5)	0.24
Strength	1.4 (0.8, 1.6)	1.1 (0.6, 1.6)	1.9 (1.4, 2.3)	0.063
Endurance	1.0 (0.6, 1.4)	0.8 (0.4, 1.2)	0.6 (0.4, 1.3)	0.47
Mixed	1.0 (0.4, 1.8)	1.1 (0.4, 1.7)	0.9 (0.5, 1.8)	1.00
Percentage of incomplete sessions	15.0 (0.0, 25.0)	11.1 (3.2, 20.8)	13.9 (1.9, 32.4)	0.96
Reasons for exercise termination, %				
Fatigue	74	62	56	
Nausea	13	21	22	
Pain	8	15	25	
Lack of motivation	15	9	0	
Time constrains	0	0	3	
Others	15	21	16	

Values are presented as median (Q1, Q3) except for reasons for exercise termination, which presents percentages.

Table 4: Impact of GC treatment on exercise adherence

Variable	GC LOW Prednisone ≤ 9 mg/kg (*n* = 36)	GC HIGH Prednisone > 9 mg/kg (*n* = 36)	*P*
Adherence to protocol (%) Reference value 3 sessions weekly	100.0 (82.8, 100.0)	84.8 (61.1, 100.0)	0.11
Adherence to protocol (%) Reference value 5 sessions weekly	65.2 (49.7, 81.4)	50.9 (36.7, 65.8)	**0.01***
Total exercise duration (min/week)	92.4 (70.1, 127.7)	71.1 (52.3, 93.3)	**0.01***
Training frequencies (sessions/week)			
Total	3.8 (2.9, 4.8)	3.2 (2.3, 3.9)	**0.02***
Strength	1.5 (0.9, 2.2)	1.1 (0.6, 1.5)	**0.02***
Endurance	0.8 (0.4, 1.1)	1.0 (0.5, 1.4)	0.16
Mixed	1.2 (0.4, 2.3)	0.8 (0.4, 1.4)	0.13
Percentage of incomplete sessions (%)	10.8 (0.0, 20.4)	16.7 (5.4, 31.2)	0.15
Reasons for exercise termination, %			
Fatigue	60	67	
Nausea	23	15	
Pain	10	19	
Lack of motivation	8	11	
Time constrains	1	0	
Others	20	17	

Abbreviations: GC LOW, Prednisone ≤9 mg/kg; GC HIGH, Prednisone >9 mg/kg
Values are presented as median (Q1, Q3) except for reasons for exercise termination, which presents percentages. *P = < 0.05.

Table 5: Impact of conditioning regimen on training response

Variable	Admission to hospital (A)	Discharge from hospital (D)	%-change A to D	ANCOVA results*	
				Adjusted difference MAC-RIC RIC-NMC MAC-NMC (95CI)	*P* MAC-RIC, RIC-NMC, MAC-NMC
	Mean (SD)	Mean (SD)	Median (Q1,Q3)		
Elbow extension (N)					
MAC (*n* = 37)	151 (54)	137 (52)	- 9.6 (-19.7, 2.7)	1.3 (-14.8, 17.4)	0.98
RIC (*n* = 60)	162 (51)	142 (49)	-11.3 (-20.8, -1.5)	2.4 (-22.3, 27.1)	0.97
NMC (*n* = 10)	149 (49)	130 (55)	-11.3 (-33.0, 3.8)	3.8 (-22.2, 29.7)	0.94
Elbow flexion (N)					
MAC (*n* = 37)	187 (60)	175 (72)	-4.8 (-16.4, 5.0)	2.2 (-20.6, 25.1)	0.97
RIC (*n* = 61)	215 (68)	191 (58)	-12.1 (-20.5, 6.3)	-4.9 (-39.2, 29.5)	0.94
NMC (*n* = 10)	193 (46)	180 (64)	-4.5 (-33.5, 8.3)	-2.7 (-38.7, 33.4)	0.98
Knee extension (N)					
MAC (*n* = 39)	283 (96)	238 (90)	-15.6 (-26.6, -1.6)	-0.9 (-31.5, 29.8)	1.00
RIC (*n* = 62)	317 (84)	261 (80)	-16.1 (-33.1, -5.2)	21.9 (-24.8, 68.6)	0.51
NMC (*n* = 10)	315 (86)	238 (94)	-20.4 (-35.7, -13.0)	21.0 (-28.6, 70.6)	0.58
Knee flexion (N)					
MAC (*n* = 39)	182 (65)	161 (61)	-10.5 (-19.1, 2.4)	-10.0 (-30.9, 11.0)	0.50
RIC (*n* = 62)	193 (49)	176 (55)	-8.3 (-21.8, 8.4)	9.0 (-23.5, 41.4)	0.79
NMC (*n* = 10)	194 (52)	167 (64)	-11.6 (-18.6, -7.9)	-1.0 (-35.2, 33.2)	1.00
Hip flexion (N)					
MAC (*n* = 39)	148 (48)	149 (64)	-8.3 (-23.2, 13.1)	2.4 (-18.1, 23.0)	0.96
RIC (*n* = 61)	169 (54)	156 (53)	-9.1 (-21.5, 5.4)	-16.4 (-47.2, 14.4)	0.42
NMC (*n* = 10)	149 (39)	158 (48)	4.9 (-10.2, 27.5)	-14.0 (-46.2, 18.2)	0.56
Distance 6MWT (m)					
MAC (*n* = 39)	553 (80)	475 (111)	-13.8 (-20.2, -7.1)	-7.2 (-45.4, 31.1)	0.90
RIC (*n* = 61)	579 (101)	490 (111)	-15.8 (-23.3, -6.3)	-45.0 (-103.9, 13.9)	0.17
NMC (*n* = 10)	585 (91)	541 (69)	-8.4 (-13.1, -2.8)	-52.2 (-114.6, 10.3)	0.12

Abbreviations: MAC, myeloablative conditioning; RIC, reduced-intensity conditioning; NMC, nonmyeloablative conditioning; N, Newton; m, meter
Values are presented as Mean (SD) and Median (Q1, Q3).
* Adjusted for baseline value, gender, age

Table 6: Impact of GC treatment on training response

Variable	Admission to hospital (A)	Discharge from hospital (D)	%-change A to D	ANCOVA results*	
				Adjusted difference GC low-GC high (95% CI)	*P*
	Mean (SD)	Mean (SD)	Median (Q1,Q3)		
Elbow extension (N)					
GC LOW (*n* = 35)	173 (45)	153 (48)	- 5.2 (-19.5, 3.8)	2.0 (-14.0, 17.9)	0.81
GC HIGH (*n* = 32)	150 (59)	134 (50)	-11.0 (-20.6, 2.9)		
Elbow flexion (N)					
GC LOW (*n* = 36)	220 (54)	206 (56)	-2.6 (-18.7, 9.5)	-3.7 (-24.5, 17.2)	0.73
GC HIGH (*n* = 31)	188 (71)	184 (68)	-0.8 (-15.5, 12.8)		
Knee extension (N)					
GC LOW (*n* = 36)	351 (59)	287 (66)	-15.8 (-28.4, -7.9)	20.6 (-10.1, 51.3)	0.19
GC HIGH (*n* = 34)	297 (86)	238 (77)	-20.9 (-36.3, -0.9)		
Knee flexion (N)					
GC LOW (*n* = 36)	207 (36)	187 (50)	-7.2 (-23.0, 3.8)	5.0 (-16.9, 26.8)	0.65
GC HIGH (*n* = 34)	187 (60)	167 (60)	-11.4 (-20.5, 8.2)		
Hip flexion (N)					
GC LOW (*n* = 36)	167 (42)	164 (51)	-0.6 (-17.8, 12.5)	4.4 (-14.9, 23.7)	0.65
GC HIGH (*n* = 33)	148 (47)	145 (53)	-5.6 (-12.3, 4.4)		
Distance 6MWT (m)					
GC LOW (*n* = 35)	602 (93)	516 (117)	-13.08 (-22.5, -4.6)	-1.4 (-40.12, 37.26)	0.94
GC HIGH (*n* = 34)	559 (96)	480 (120)	-14.43 (-23.9, -6.3)		

Abbreviations: GC LOW, Prednisone ≤9mg/kg; GC HIGH, Prednisone>9mg/kg; N, Newton; m, meter
Values are presented as mean (SD) and Median (Q1,Q3).
*Adjusted for baseline value, gender and age