Doctoral thesis submitted to
the Faculty of Behavioural and Cultural Studies
Heidelberg University
in partial fulfillment of the requirements of the degree of
Doctor of Philosophy (Dr. phil.)
in Sport Science

Title of the publication-based thesis

Improving exercise prescriptions for hematological cancer patients during and after allogeneic stem cell transplantation. Conclusions from two large randomized controlled trials.

presented by
Rea Maria Kühl

year of submission
2015

Dean: Prof. Dr. Klaus Fiedler
Advisor: Prof. Dr. Gerhard Huber

This dissertation is based on the following publications

I Wiskemann J, Kuehl R, Dreger P, Schwerdtfeger R, Huber G, Ulrich CM, Jaeger D, and Bohus M. *Efficacy of exercise training in SCT patients – who benefits most?* Bone Marrow Transplantation. 2014; 49:443-8.

II Wiskemann J*, Kuehl R,* Dreger P, Huber G, Kleindienst N, Ulrich CM, Bohus M. *Physical Exercise Training versus Relaxation in Allogeneic stem cell transplant patients (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.* (submitted to BMC Cancer, June 2015) *shared first authorship

III Kuehl R, Scharhag-Rosenberger F, Schommer K, Schmidt ME, Dreger P, Huber G, Bohus M, Ulrich CM, Wiskemann J. *Exercise intensity classification in cancer patients undergoing allogeneic HCT*. Med Science Sport & Exercise, 2015; 47(5):889-95.

IV Kuehl R, Schmidt ME, Dreger P, Steindorf K, Bohus M, Wiskemann J. *Determinants of exercise adherence in cancer patients during and after allogeneic HCT* (submitted to Med Science Sport & Exercise, June 2015)

This dissertation is based on two large randomized controlled exercise intervention trials in hematological cancer patients during and after allogeneic stem cell transplantation and comprises four manuscripts. The first manuscript is based on a recently finished trial (main findings published in Blood 2011 by Wiskemann et al.). The other manuscripts are based on a currently ongoing trial. This study (PETRA study) is conducted at the National Center for Tumor Diseases (NCT) Heidelberg in cooperation with the Heidelberg University Hospital. The author of this dissertation has a leading position for study coordination and is overseeing all study procedures. Both studies were funded by the Deutsche José Carreras Leukämie Stiftung e.V. (No: R10/42pf and R05/33p). The PETRA study is registered at ClinicalTrials.gov, No: NCT01374399.

Further peer-reviewed publications

Scharhag-Rosenberger F, Kuehl R, Klassen O, Schommer K, Schmidt ME, Ulrich CM, Wiskemann J*, Steindorf K.* *Exercise training intensity prescription in breast cancer survivors: validity of current practice and specific recommendations.* J Cancer Surviv, 2015.

*shared last authorship

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.

*shared first authorship

Book Chapter

In German

Wiskemann J, Nies R, Vandenbergh D. (2012): Kapitel 18 - *Leukämien und Lymphome*. In: Körperliche Aktivität und Sport bei Krebs. Baumann, Jäger, Bloch (Hrsg.) Springer, Heidelberg, 189-208.

Abstract

The evidence of exercise as adjuvant therapy option in cancer patients is increasing. Exercise constitutes a promising intervention to reduce treatment-related side-effects and to improve the rehabilitation process. Thus, there is growing interest in determining optimally targeted exercise prescriptions to maximize effects. However, few randomized controlled trials (RCTs) were conducted in haematological cancer patients during and after allogeneic stem cell transplantation (allo-HCT). Consequently, information regarding detailed exercise prescriptions and exercise response is lacking. Furthermore, a detailed description of adherence and related determinants would improve the understanding of exercise participation.

The aim of this cumulative thesis is therefore to further close the indicated research gaps. Four manuscripts constitute the main body of this work. In these we (I) determined the individual training response dependent on physical performance level at baseline; we (II) described a large randomized controlled exercise intervention trial (PETRA study); we (III) compared recommended endurance exercise intensity classes to values obtained in haematological cancer patients; and we (IV) pictured adherence and its determinants in different treatment periods as well as the physical activity level of the control group within the PETRA study. Additionally, this thesis translates the findings into the current research context in the discussion part. The results will further refine exercise recommendations and exercise programs and will give important information for future study designs and data interpretation.

(I) The first manuscript analysed data from 52 patients randomized to the experimental group in an RCT prior to, during and after allo-HCT. Results show that initially *unfit* patients had a significant better development of muscle strength and endurance performance during intervention period than the initially *fit* patients. For example, *fit* patients lost 31% of their knee extensor strength, whereas *unfit* patients lost only 1% ($p=.03$). For endurance capacity, the initially *fit* patients lost 4%, whereas the *unfit* patients gained 13% ($p<.01$). This finding is of major clinical relevance because exercise is often not recommended in deconditioned patients.

(II) The second manuscript describes the PETRA study design. In this RCT, 256 patients prior to allogeneic stem cell transplantation will be included. The primary endpoint will be overall-survival after two years. Secondary endpoints include physical performance, fatigue, quality of life, severity of side-effects and biomarkers. Gold-standard assessment procedures to assess physical performance and physical activity will be applied. The experimental group performs a partly supervised one-year combined (endurance and resistance training) moderate-intensity exercise program, the control group receives a comparable intervention, but with progressive muscle relaxation. The PETRA study will provide a large database to investigate the multidimensional effects of exercise on various clinical outcomes.

(III) In the third manuscript we compared for the first time commonly used endurance exercise intensity classes from the American College of Sports Medicine (ACSM) with cardiopulmonary exercise data obtained in a cancer population (106 patients prior to and 180 days after allo-HCT). The analysis revealed that the ACSM's exercise intensity recommendations for endurance training might not meet the targeted intensity classes in almost all classes ($p<.05$). The use of ACSM's intensity classes would result in over- or under-estimation of endurance exercise intensity in allo-HCT patients. In order to give appropriate exercise prescriptions and to compare intensities between other studies, we provided tables with exercise intensity classes obtained in haematological cancer patients. Furthermore, we revealed that applying exercise intensity recommendations based on percentages of the commonly used equation *220-age* did not provide appropriate intensities, and is therefore, not recommended. We expect that our results will further improve exercise prescription in haematological cancer patients.

(IV) The fourth manuscript examined exercise adherence and physical activity in the control group (contamination) including the first 153 patients of the PETRA study. With 66-77% (89–199 min/ week) adherence was acceptable in all three studied periods (inpatient, outpatient up to day 100, day 100 up to day 180). Most important determinants for adherence were fatigue ($p=.004$), physical performance ($p=.003$) and prior exercise engagement ($p=.010$) in different studied periods. The models could explain 16%, 21% and 55% of variance respectively. Exercise contamination in the control group was evident in 54% (89% were walking on a regular basis). Determinants for exercise contamination were higher muscle strength ($p=.025$) and less fatigue ($p=.050$). Total variance explained was 29%. The recruitment of the first 153 patients in the PETRA study was excellent (73%), providing us with a representative sample of this challenging population. The results give important implications for personalized exercise programs and future data interpretation.

In conclusion, this cumulative thesis gives essential information regarding questions on how to individually tailor exercise interventions for haematological cancer patients. Furthermore, the identification of determinants of both, adherence to exercise intervention and contamination of the control group will improve exercise programs and illustrate the need to pay more attention on physical activities performed in the control groups.

Kurzzusammenfassung

Die Evidenz zu körperlichen Trainingsprogrammen als unterstützende Maßnahme bei Krebserkrankungen nimmt zu. Das körperliche Training stellt hierbei eine vielversprechende Intervention dar, um behandlungsbedingte Nebenwirkungen zu reduzieren und den Rehabilitationsprozess zu verbessern. Daher besteht zur optimalen Nutzung der positiven Effekte von körperlichem Training ein wachsendes Interesse darin, bestmögliche Trainingsempfehlungen für Patienten zu entwickeln. Im Bereich der Hämato-Onkologie wurden bisher jedoch nur wenige randomisierte, kontrollierte Studien (RCTs) mit Patienten während und nach einer allogenen Stammzelltransplantation (allo-HCT) durchgeführt. Informationen zu detaillierten Trainingsempfehlungen und Trainingsansprechen sind dementsprechend mangelhaft. Darüber hinaus würde eine detaillierte Beschreibung der Trainingsadhärenz und ihrer Determinanten helfen, die Akzeptanz des Trainings durch die Patienten zu verstehen.

Das Ziel dieser kumulativen Thesis ist es, diese Forschungslücke weiter zu schließen. Vier Manuskripte bilden dabei den Hauptteil dieser Arbeit. Es wurde (I) das individuelle Trainingsansprechen in Abhängigkeit von der körperlichen Fitness vor der Intervention (zu Baseline) erfasst; (II) eine große randomisierte, kontrollierte Trainings-Interventionsstudie (PETRA Studie) beschrieben, (III) empfohlene Ausdauertrainingsintensitätsklassen zu Intensitätswerten von hämato-onkologischen Patienten verglichen; und (IV) Trainingsadhärenz und ihre Determinanten in verschiedenen Behandlungsphasen, sowie das körperliche Aktivitätslevel der Kontrollgruppe in der PETRA Studie beschrieben. Zusätzlich wurden in der gemeinsamen Diskussion die Ergebnisse der verschiedenen Untersuchungen in den aktuellen Forschungszusammenhang gesetzt. Die Ergebnisse werden dabei helfen, Trainingsempfehlungen und körperliche Trainingsprogramme zu verfeinern, und bringen wichtige Erkenntnisse für zukünftige Studiengestaltung und Interpretation von Ergebnissen.

(I) Das erste Manuskript untersucht Daten von 52 Patienten aus der Experimentalgruppe einer RCT vor, während und nach allo-HCT. Ergebnisse zeigten, dass zu Beginn *unfitte* Patienten eine signifikant bessere Entwicklung von Muskelkraft und Ausdauer während der Intervention hatten, als die initial *fitten* Patienten. Zum Beispiel verloren die *fitten* Patienten 31% ihrer Knie-Extensor-Kraft, während die initial *unfitten* Patienten nur 1% verloren ($p=.03$). Bezüglich der Ausdauerleistung verloren die *fitten* Patienten 4%, während sich die *unfitten* Patienten um 13% verbesserten ($p<.01$). Dieses Ergebnis ist von großer klinischer Relevanz, da körperliches Training den eher *unfitten* Patienten meist nicht empfohlen wird.

(II) Das zweite Manuskript beschreibt die PETRA Studie. In diese randomisierte, kontrollierte Studie werden 256 Patienten vor Beginn einer allo-HCT eingeschlossen. Primärer Endpunkt ist das Gesamtüberleben nach zwei Jahren. Sekundäre Endpunkte sind körperliche Fitness, Fatigue, Lebensqualität, Schwere der Nebenwirkungen und Biomarker. Zur Erhebung von körperlicher Fitness und körperlicher Aktivität werden Gold-Standard-Methoden eingesetzt. Die Experimentalgruppe führt ein teilweise supervidiertes, einjähriges körperliches

Trainingsprogramm, bestehend aus moderatem Kraft- und Ausdauertraining durch; die Kontrollgruppe erhält mit progressiver Muskelentspannung eine vergleichbare Intervention. Die PETRA Studie wird eine umfangreiche Datenbasis bereitstellen, um die multidimensionalen Effekte von körperlichem Training auf verschiedenste klinische Endpunkte hin zu untersuchen.

(III) Das dritte Manuskript vergleicht erstmals die vom American College of Sports Medicine (ACSM) empfohlenen Ausdauertrainings-Intensitätsklassen mit Spiroergometriedaten von Krebspatienten (106 Patienten, vor und 180 Tage nach allo-HCT). Die Analyse zeigte, dass die Intensitäts-Empfehlungen des ACSM in nahezu fast allen Trainingsintensitäten nicht den angestrebten Intensitätsklassen, z.B. von moderater Intensität, entsprechen ($p>.05$). Die Verwendung der ACSM Empfehlungen würde zu einer Über- bzw. Unterschätzung der Trainingsintensität bei allogen stammzelltransplantierten Patienten führen. Des Weiteren entwickelten wir Tabellen, die zur Empfehlung einer adäquaten Trainingsintensität und zu Vergleichen von bereits durchgeführten Trainingsintensitäten in verschiedenen Studien herangezogen werden können. Zusätzlich untersuchten wir, ob die häufig verwendete Formel *220-Lebensalter* zur Maximalpulsbestimmung bei Patienten vor und nach allogener Stammzelltransplantation verwendet werden kann. Wir fanden heraus, dass sich anhand dieser Formel keine adäquaten Trainingsintensitäten ableiten lassen. Mit unseren Ergebnissen ist eine bessere Trainingsintensitätsvorgabe für hämatologische Krebspatienten möglich.

(IV) Das vierte Manuskript untersucht die Trainingsadhärenz und körperliche Aktivität der Kontrollgruppe der ersten 153 Patienten der PETRA Studie. Die Adhärenz war mit 66 bis 77% (89-199 Minuten pro Woche) in allen drei untersuchten Studienphasen (stationär, nach Entlassung bis Tag 100 und Tag 100 bis 180) akzeptabel. Wichtigste Determinanten der Adhärenz in den verschiedenen Studienphasen waren Fatigue ($p=.004$), körperliche Leistungsfähigkeit ($p=.003$) und sportliche Aktivität vor der Transplantation ($p=.010$). Die Modelle konnten 16%, 21% bzw. 55% der Varianz erklären. 54% der Patienten in der Kontrollgruppe waren nach der Transplantation (Tag 180) sportlich aktiv (89% gaben an, regelmäßig spazieren zu gehen). Determinanten für eine Kontamination in der Kontrollgruppe waren höhere Muskelkraft ($p=.025$) und weniger Fatigue ($p=.050$). Insgesamt konnten durch das Modell 29% der Varianz erklärt werden. Die Rekrutierungsrate der ersten 153 Patienten der PETRA Studie war sehr gut (73%), so dass wir von einer repräsentativen Stichprobe in dieser herausfordernden Population ausgehen können. Die Ergebnisse dieser Untersuchung geben wichtige Hinweise zu personalisierten Trainingsvorgaben und für die weitere Interpretation von Studiendaten.

Diese kumulative Thesis stellt grundlegende Informationen hinsichtlich der Frage zur Verfügung, wie ein körperliches Trainingsprogramm bei hämato-onkologischen Patienten individuell angepasst werden kann. Des Weiteren hilft die Identifikation der Determinanten von Trainingsadhärenz und Kontamination zukünftige Trainingsprogramme zu verbessern. Darüber hinaus zeigen die Ergebnisse, dass der körperlichen Aktivität der Patienten in der Kontrollgruppe mehr Aufmerksamkeit geschenkt werden muss.

Contents

List of Abbreviations

ACSM	American college of sports medicine
Allo-HCT	allogeneic hematopoietic stem cell transplantation
CPET	cardiopulmonary exercise test
GvHD	graft versus host disease
HR_{max}	maximum heart rate
HRR	heart rate reserve
P	probability of error
P_{max}	peak power output
PEACE	Physical Exercise Across the Cancer Experience
PROs	patient reported outcomes
RCTs	randomized controlled trials
SD	standard deviation
VO_{2max}	maximal oxygen uptake
$VO_{2reserve}$	oxygen uptake reserve

List of Figures

1 General Introduction

Cancer is the second most common cause of death in Western countries, including Germany. Despite continually improved treatment options, the different treatment modalities are associated with a variety of adverse physical and psychosocial symptoms, leading to low physical function, increased fatigue levels, anxiety and depression. These distressing symptoms affect patients' quality of life during treatment as well as up to years after treatment. In recent years, complementary therapy approaches received more and more attention. However, high prevalence of side-effects and complications and severe impact of treatment are enormous challenges for implementing exercise interventions in cancer patients. Regardless of these difficulties, the rationale for exercise and physical activity interventions in cancer patients has been established (1, 2), and results from randomized controlled trials (RCTs) provide clear evidence that exercise interventions in cancer patients during and after treatment are safe and lead to various beneficial effects (2-7). Due to their multidimensional effectiveness, exercise interventions proved to be effective not only on physical performance, but also on psychological outcomes, for example cancer- related fatigue (8-10). Overall, there is established evidence that exercise has positive effects on quality of life during and after treatment (11, 12).

Courneya and Friedenreich published 2001 an organizational model for examining physical exercise across the cancer continuum, entitled Physical Exercise Across the Cancer Experience (PEACE). PEACE devides the cancer trajectory in 2 prediagnosis (prescreening and screening) and 4 postdiagnosis (pretreatment, treatment, posttreatment and resumption) periods, where exercise has a logic role (see figure 1). For exercise intervention studies, the last three periods are most important and cover coping, rehabilitation/ palliatation, health promotion and survival phase (13). It should be noted that there is evidence from epidemiological research that physical activity can reduce the risk of developping some cancers e.g. breast and colon cancer (14). For heamatological malignancies, however, no clear association could be found (15, 16).

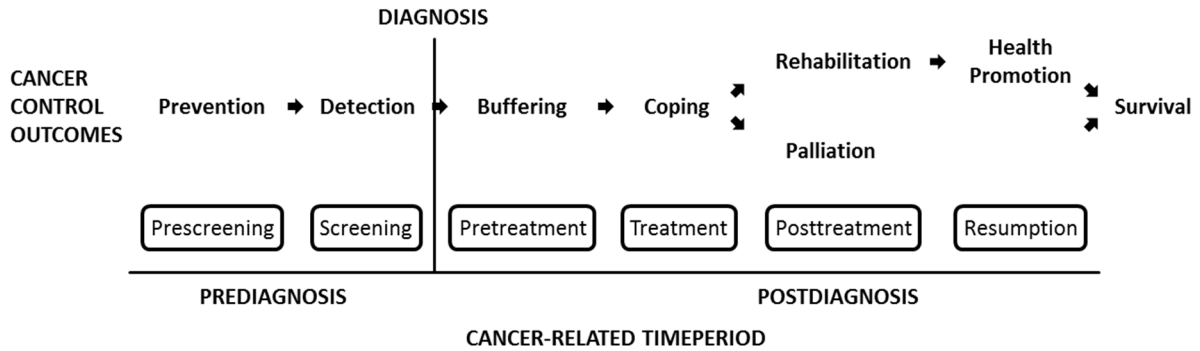

Figure 1: PEACE Framework. An organizational model for examining physical exercise across the cancer experience (13).

Jones and Alfano recently reviewed the current literature using the PEACE framework in order to gain an overview about the current research state in the exercise oncology field and to define important reasearch gaps. They concluded that a solid platform exists to launch next generation studies, necessary to answer questions concerning optimal dose, individual response, and adherence. However, they also raised concerns about problems associated with control groups and recruitment (17). These issues/ aspects will be the central subjects of this thesis. However, in the field of oncology research, the majority of studies addressed the effects of exercise interventions in breast cancer patients, and only few RCTs were performed in hematological cancer patients during and after allogeneic stem cell transplantation (allo-HCT). Therefore, the effectiveness of exercise interventions in allo-HCT patients has not yet been fully established. Furthermore, practical implications, regarding exercise guidelines for hematological cancer patients are missing.

General guidelines for exercise prescription in healthy subjects are well defined, including the principle components of systematic individualized exercise: mode, intensity, duration, frequency and progression (18-21). Intensity is considered as the most important one (19), and higher intensity levels are more effective in increasing fitness outcomes (22, 23). As a consequence of the growing number of studies in the field of exercise and cancer in the last years, a number of exercise recommendations for cancer patients have been published. The most influential one is the American College of Sports Medicine (ACSM) roundtable on exercise guidelines for cancer survivors by Schmitz et al. (24). This guideline gives a broad overview on the current evidence of beneficial effects and exercise recommendations for different entities, it gives advice on how to deal with side-effects and points out contraindications for exercise. There was consensus that international guidelines for healthy people are generally appropriate for cancer survivors, with the additional note that programs may need to be adapted depending on the clinical status of the individual patient. Thus, it is recommended to be active with moderate activity for 150min per week or vigorous activity for 75min per week (24). The Australian guidelines give more specific exercise prescriptions, e.g. intensities, but the evidence for the given recommendations remains unclear. The authors concluded that there is no evidence concerning the upper and lower thresholds of exercise required to achieve benefits and the type of exercise preferred (25). For hematological cancer patients undergoing HCT particular resistance exercise is suggested. Furthermore, it is recommended to start with lighter intensity and slower progression and to gradually built up intensity and duration (26). Overall, the guidelines remain very unspecific, and important questions concerning dose (intensity), timing and content of an exercise program remain unanswered.

Buffart et al. summarized and discussed available exercise guidelines for cancer survivors. The authors pointed out that problems with program participation and adherence existed. They concluded that a ‘one-size-fits-all’ approach did not seem to work in a heterogeneous group of cancer patients, and the researchers recommended that prescriptions should be individually tailored to the individual characteristics, needs and capabilities of every single

patient. Accordingly, the aim should be to develop specific guidelines to describe a given exercise intervention with mode/ type, frequency, intensity and duration. In addition, the particular phases of cancer trajectory (PEACE framework) should be considered (27).

In order to enhance exercise prescriptions in hematological cancer patients this thesis approaches two issues: In chapter 2 we will address the question whether allo-HCT patients with different initial fitness levels prior transplantation respond differently to an exercise intervention during and after transplantation. In chapter 4, a comparison of given ACSM endurance exercise intensities with intensity classes obtained in hematological cancer patients will be presented in order to investigate, if the used exercise intensities for endurance training prescription are valid in cancer patients. Both contributions will have an impact on the practical implications of exercise prescription in allo-HCT patients.

Beside the development of more specific guidelines it is of interest, if patients can adhere to the given exercise prescription. Adherence is described as the degree to which a patient is able to follow the exercise prescription. Only the detailed knowledge of the exercise dose received (adherence) allows for correct interpretation of findings and dose-response effects and provides information on tolerability and safety. Winters-Stone et al. reviewed reporting of adherence to the principles of exercise training, the FITT formula. FITT symbolizes frequency, intensity, type and timing of exercise interventions. The researchers concluded that the reporting of the FITT criteria regarding adherence is lacking. They stated that it might be possible that any null trials were the result of not only poorly designed, but also poorly delivered interventions rather than a lack of efficacy. They recommend describing adherence based on all FITT components (28). Consequently, a recent review summarized the adherence in 20 studies (including 998 patients) following hematopoietic stem cell transplantation. Adherence was little reported, with the majority of supervised studies reporting no adherence rates at all. Furthermore, the authors pointed out that for translating exercise programs into clinical practice it is crucial to include information about attrition. Attrition is described as the proportion of participants who failed to complete the research activities or withdrew from study. The overall attrition was 18% (range 0-44%), and major reasons for attrition included death and change in health status. Since the overall retention rate was high (82%), the authors concluded that this reflected the acceptance of exercise and the ability to tailor exercise intervention appropriately (29). However, high retention rates might also occur when a selective and/or small sample is included, for example, only patients with few side-effects and adverse symptoms who are motivated to exercise. Therefore, attention to the amount of screened patients and the recruitment rate need to be put in comparison to the total population of patients. Only this additional information will ensure a correct interpretation of findings and allow for generalisability.

Moreover, an adoption of exercise behavior in the control group (exercise contamination) is a little studied topic in exercise intervention trials. Exercise contamination is only described in very few studies and the extent to which it influences the findings is unknown (30-32). However, knowledge about determinants of both, adherence and contamination will improve

design of future intervention programs and interpretation of study results. Chapter 5 will cover the aspects of adherence, contamination, recruitment and retention in the PETRA study. The PETRA study is a large RCT during and after allo-HCT and will be described in detail in chapter 3. Problems associated with allo-HCT will be described in the next section.

1.1 Allogeneic Stem Cell Transplantation

Allogeneic stem cell transplantation is an established procedure to treat various hematological diseases in high-risk situations, e.g. leukemias, lymphomas and plasma cell disorders. This demanding treatment is, however, associated with a large variety of treatment-related side-effects and complications, leading to physical and psychosocial morbidity. Overall, about 40 percent of patients with advanced hematological cancers who undergo allo-HCT die from complications (33). In 2011, more than 14,000 patients in Europe received an allo-HCT, main indications were leukemias (34). In Germany, 2.6% of all new cancer cases in men (and 2.2% in women) are attributed to leukemia and 3.3% of all cancer-specific deaths belong to patients with this type of cancer. Even though survival rates have substantially improved over the past decades, the 5-year survival rate for leukemia is about 50%, and only in very few cases real cure can be assumed (35).

In the past 10 years, the overall number of allo-HCT has doubled (34). The recent development of reduced-intensity conditioning-chemotherapy prior allo-HCT resulted in a minimization of the toxicity, and has consequently led to a reduced early non-relapse mortality. For this reason, more elderly and multimorbid patients, normally not considered for allo-HCT, could be treated with transplantation (36, 37). Nonetheless, graft-versus-host disease (GvHD), an immune response (autoimmune reaction), induced by donor T-cells targeting patient's tissues, e.g. mucosa, skin and lung remains a major complication after allo-HCT. Severe GvHD has a poor prognosis with a 5-year-survival of only 25%. Chronic GvHD is the major cause of morbidity and transplant-related mortality after allo-HCT (33, 38). However, new treatments and improved supportive care lead to improved prognosis and an increased life expectancy. Consequently, supportive treatments that improve quality of life and re-integration in social life are needed.

Transplant-related morbidity is evident throughout the whole course of an allo-HCT, from pre-transplant conditioning, extending in long-term survivorship after HCT. The occurrence of complications and side-effects depends on the treatment period. A large proportion of patients present physical deficits already prior to transplantation. In a prospective observational study 50% of all 164 patients experienced sacropenia (measured via bio-impedance analysis). Sacropenia was associated with decreased muscle strength, increased fatigue, and lower physical functioning scores (39). A prospective cohort study including 59 patients showed that in 39% hand grip strength was below 80% of predicted values and the submaximal endurance capacity (six-minute walk distance) was reduced in 58% of patients

(40). Additionally, another study in 110 patients prior allo-HCT confirmed these findings (41). A recent review about muscle dysfunction in cancer patients summarized that muscle dysfunction is a common side-effect across all stages of cancer trajectory, and it was negatively associated with clinical endpoints, e.g. quality of life, complications and mortality (42). Furthermore, cancer cachexia, described as an excessive body weight loss, is known to be associated with poor prognosis (43, 44).

The conditioning chemotherapy in preparation for allo-HCT (in some cases high-dose chemotherapy and/ or total body irradiation) suppresses the immune system, leading to a high risk of infections (e.g. pneumonia, sepsis) due to a phase of aplasia. This condition requires prolonged periods of isolation in single bedrooms in laminar airflow units, until the haematological system has recovered. Moreover, mucositis, diarrhoea, nausea, vomiting and pain are frequent adverse symptoms in this phase (45, 46).

As already mentioned, a major complication after allo-HCT is GvHD. Even though, chronic GvHD occurs in about 50% of patients, the pathophysiology is poorly understood (47). Chronic GvHD has been shown to be associated with a lower physical performance and functional capacity (48). In one study in 584 long term survivors, individuals with active chronic GvHD (about 50%) had a significant impact on many aspects of overall health status, including functional impairments and activity limitation (49). High-dose steroids are the first line treatment for GvHD, but they are associated with a variety of adverse side-effects, including steroid myopathy. One retrospective study in 70 patients with acute GvHD under high-dose steroid treatment could demonstrate that 41% of patients developed a moderate steroid myopathy. Furthermore, the myopathy was associated with a moderate to severe degree of functional impairment. (50) Moreover, glucocorticosteroids are well known to induce muscle wasting (51). In an observational cohort study in 113 allo-HCT patients, the total corticosteroid dose was correlated with a decrease of hand-grip and knee-extensor strength (52). Furthermore, bed rest studies have shown the negative impact of inactivity on muscle performance (53), exacerbating the problem of deconditioning and loss of muscle mass given the low activity levels of patients described below.

Recent literature has shown that patients after HCT are likely to have long-term difficulties with physical functioning, problems with fatigue, distress and psychological well-being. These quality-of-life and transplanted-related concerns can be present years after transplantation (54-56). Furthermore, patients after allo-HCT are at an increased risks of cardiovascular events and pulmonary complications (57-59). Some large observational studies exist that examined the impact of transplantation years after treatment on different quality of life outcomes. Andrykowski et al. recruited survivors through international registries (n=662) and assessed a range of patient reported outcomes (PROs) e.g. physical, psychological and social functioning via telephone interview. Data were compared with matched healthy controls. HCT survivors were at a mean of 7 years after transplantation (1.8 to 22.6 years range) and reported an overall poorer health status regarding physical health, physical functioning, social functioning, well-being and fatigue (mean effect size for all 24 outcomes

was 0.36 standard deviations (SD)) as matched healthy controls. For physical variables, largest effect sizes were observed (mean effect size 0.47 SD), whereas the social functioning cluster was less affected (mean effect size 0.18 SD). Interestingly, survivors reported more psychological and interpersonal growth (60).

Knowing that a large proportion of side- and late-effects are associated with low physical activity levels (61), some studies assessed the physical activity behavior in hematological cancer entities. One study in 319 survivors of aggressive non-Hodgkin's Lymphoma revealed that 2-5 years after diagnosis 53% of survivors were less active than the recommended 150 minutes per week, 20% reported no physical activity at all. Interestingly, individuals who met guidelines reported better quality of life. Also, a significant dose-response pattern between activity and mental and physical health could be observed (62). This finding was consistent with another retrospective study in 156 multiple myeloma patients, where exercise during and after treatment was significantly positively associated with various subdomains of quality of life (63). Another study in 352 cancer survivors ascertained that not the absolute amount of exercise was most important in influencing quality of life, but the change of exercise behavior after cancer diagnosis. Survivors who maintained or increased activity levels had a significantly higher quality of life (64). In comparison to current guidelines, Valance et al. described that 23.7% of 438 non-Hodgkin's Lymphoma patients met exercise guidelines (150 min activity per week) off treatment, whereas only 6.5% of this population was sufficiently active during treatment (65). However, because these were observational studies, there is no causal relationship between health and physical activity. Furthermore, the data were measured via self-report and it is well-known that individuals overestimate activity levels when asked (66). In conclusion, general activity levels of hematological cancer patients were low, requiring effective strategies to enhance activity.

1.2 Exercise in Stem Cell Transplantation

Emerging evidence indicates positive benefits of exercise intervention in the context of HCT. Previous studies demonstrated that exercise might significantly improve physical performance, quality of life, symptom control and fatigue in different time points during and after HCT (67-72). However, only eight RCTs could be included in the most recent review on exercise studies in the HCT setting. Of these trials, only 6 studies included allo-HCT patients, and 3 studies examined effects of exercise exclusively in allo-HCT patients (68). As an example, Jarden et al. should be mentioned who investigated a supervised multimodal exercise program during hospital stay in allo-HCT patients. The exercise program consisted of endurance exercise five times per week (15-30 min cycling, >75% HR_{max}) and resistance exercise three times per week (15-20 min). The control group received physiotherapy (up to 1.5 hours per week). Of 42 included patients, 34 completed the study. Adherence was high with 80% of all scheduled cycling sessions and 98% of all resistance training sessions attended. Significant group differences could be found at discharge for the primary endpoint

maximum oxygen uptake (VO_{2peak}), muscle strength and some side-effects e.g. diarrhoea (73, 74). In another trial, Mello et al. started their supervised aerobic exercise program (up to 40 min walking on a treadmill, >70% HR_{max}, five times per week) after discharge. 18 patients after allo-HCT were included, but no adherence data were reported for the 9 exercise group participants. Significant effects could be found for different tested muscle groups (75). Another large RCT recruited 131 patients (80 autologous HCT and 51 allo-HCT patients). The 12-week outpatient supervised intervention started after transplantation (median 79 days after HCT) and consisted of 20 min aerobic training (50-80%HR_{max}) and resistance exercises. Adherence was described as attendance (85%). 114 participants completed the study, and significant effects were found for physical performance outcomes. It should be noted that this study did not included patients with GvHD occurrence (76). The largest RCT in the field of allo-HCT so far has been the study by Wiskemann et al. The researchers included 105 patients prior allo-HCT. The intervention program started two to three weeks before admission, and lasted up to eight weeks after discharge. The exercise program consisted of a mix of endurance and resistance exercises and was partly supervised (supervised two times per week during inpatient period, weekly phone calls during outpatient setting). The control group received the same amount of social contact (visits in hospital and telephone calls) to minimize bias regarding social contact. The intervention significantly improved the primary outcome fatigue as well as physical performance and distress (77). In addition, a retrospective analysis of two-year survival data of this study revealed potential positive effects of exercise on overall mortality and non-relapse mortality. However, this was a post-hoc analysis and the study was not designed/ powered for this endpoint (78). Consequently, the PETRA study was designed. This new study will give a unique opportunity to examine effects of a one-year exercise intervention on overall survival, treatment related side-effects and complications during and after allo-HCT (see chapter 3 and 5).

1.3 References

1. Irwin ML. Physical activity interventions for cancer survivors. *Br J Sports Med*. 2009;43(1):32-8.
2. Lakoski SG, Eves ND, Douglas PS, and Jones LW. Exercise rehabilitation in patients with cancer. *Nat Rev Clin Oncol*. 2012;9(5):288-96.
3. Ferrer RA, Huedo-Medina TB, Johnson BT, Ryan S, and Pescatello LS. Exercise interventions for cancer survivors: a meta-analysis of quality of life outcomes. *Ann Behav Med*. 2011;41(1):32-47.
4. Fong DY, Ho JW, Hui BP, Lee AM, Macfarlane DJ, Leung SS, Cerin E, Chan WY, Leung IP, Lam SH, Taylor AJ, and Cheng KK. Physical activity for cancer survivors: meta-analysis of randomised controlled trials. *BMJ*. 2012;344:e70.
5. Stene GB, Helbostad JL, Balstad TR, Riphagen, II, Kaasa S, and Oldervoll LM. Effect of physical exercise on muscle mass and strength in cancer patients during treatment--a systematic review. *Crit Rev Oncol Hematol*. 2013;88(3):573-93.
6. Strasser B, Steindorf K, Wiskemann J, and Ulrich CM. Impact of resistance training in cancer survivors: a meta-analysis. *Med Sci Sports Exerc*. 2013;45(11):2080-90.
7. Jones LW, Liang Y, Pituskin EN, Battaglini CL, Scott JM, Hornsby WE, and Haykowsky M. Effect of exercise training on peak oxygen consumption in patients with cancer: a meta-analysis. *Oncologist*. 2011;16(1):112-20.
8. Brown JC, Huedo-Medina TB, Pescatello LS, Pescatello SM, Ferrer RA, and Johnson BT. Efficacy of exercise interventions in modulating cancer-related fatigue among adult cancer survivors: a meta-analysis. *Cancer Epidemiol Biomarkers Prev*. 2011;20(1):123-33.
9. Cramp F, and Byron-Daniel J. Exercise for the management of cancer-related fatigue in adults. *Cochrane Database Syst Rev*. 2012;11:CD006145.
10. Al-Majid S, and Gray DP. A biobehavioral model for the study of exercise interventions in cancer-related fatigue. *Biol Res Nurs*. 2009;10(4):381-91.
11. Mishra SI, Scherer RW, Snyder C, Geigle PM, Berlanstein DR, and Topaloglu O. Exercise interventions on health-related quality of life for people with cancer during active treatment. *Cochrane Database Syst Rev*. 2012;8:CD008465.
12. Mishra SI, Scherer RW, Geigle PM, Berlanstein DR, Topaloglu O, Gotay CC, and Snyder C. Exercise interventions on health-related quality of life for cancer survivors. *Cochrane Database Syst Rev*. 2012;8:CD007566.
13. Courneya KS, and Friedenreich CM. Framework PEACE: an organizational model for examining physical exercise across the cancer experience. *Ann Behav Med*. 2001;23(4):263-72.
14. Friedenreich CM, Neilson HK, and Lynch BM. State of the epidemiological evidence on physical activity and cancer prevention. *Eur J Cancer*. 2010;46(14):2593-604.
15. Vermaete NV, Wolter P, Verhoef GE, Kollen BJ, Kwakkel G, Schepers L, and Gosselink R. Physical activity and risk of lymphoma: a meta-analysis. *Cancer Epidemiol Biomarkers Prev*. 2013;22(7):1173-84.
16. Walter RB, Buckley SA, and White E. Regular recreational physical activity and risk of hematologic malignancies: results from the prospective VITamins And lifestyle (VITAL) study. *Ann Oncol*. 2013;24(5):1370-7.
17. Jones LW, and Alfano CM. Exercise-oncology research: past, present, and future. *Acta Oncol*. 2013;52(2):195-215.
18. Warburton DE, Nicol CW, and Bredin SS. Prescribing exercise as preventive therapy. *CMAJ*. 2006;174(7):961-74.
19. Garber CE, Blissmer B, Deschenes MR, Franklin BA, Lamonte MJ, Lee IM, Nieman DC, Swain DP, and American College of Sports M. 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.

20. Haskell WL, Lee IM, Pate RR, Powell KE, Blair SN, Franklin BA, Macera CA, Heath GW, Thompson PD, and Bauman A. Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. *Med Sci Sports Exerc*. 2007;39(8):1423-34.
21. Kohrt WM, Bloomfield SA, Little KD, Nelson ME, Yingling VR, and American College of Sports M. American College of Sports Medicine Position Stand: physical activity and bone health. *Med Sci Sports Exerc*. 2004;36(11):1985-96.
22. Swain DP. Moderate or vigorous intensity exercise: which is better for improving aerobic fitness? *Prev Cardiol*. 2005;8(1):55-8.
23. Duncan GE, Anton SD, Sydeman SJ, Newton RL, Jr., Corsica JA, Durning PE, Ketterson TU, Martin AD, Limacher MC, and Perri MG. Prescribing exercise at varied levels of intensity and frequency: a randomized trial. *Arch Intern Med*. 2005;165(20):2362-9.
24. Schmitz KH, Courneya KS, Matthews C, Demark-Wahnefried W, Galvao DA, Pinto BM, Irwin ML, Wolin KY, Segal RJ, Lucia A, Schneider CM, von Gruenigen VE, and Schwartz AL. American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. *Med Sci Sports Exerc*. 2010;42(7):1409-26.
25. Hayes SC, Spence RR, Galvao DA, and Newton RU. Australian Association for Exercise and Sport Science position stand: optimising cancer outcomes through exercise. *J Sci Med Sport*. 2009;12(4):428-34.
26. Wolin KY, Schwartz AL, Matthews CE, Courneya KS, and Schmitz KH. Implementing the exercise guidelines for cancer survivors. *J Support Oncol*. 2012;10(5):171-7.
27. Buffart LM, Galvao DA, Brug J, Chinapaw MJ, and Newton RU. Evidence-based physical activity guidelines for cancer survivors: current guidelines, knowledge gaps and future research directions. *Cancer Treat Rev*. 2014;40(2):327-40.
28. Winters-Stone KM, Neil SE, and Campbell KL. Attention to principles of exercise training: a review of exercise studies for survivors of cancers other than breast. *Br J Sports Med*. 2014;48(12):987-95.
29. Hacker ED, and Mjukian M. Review of attrition and adherence in exercise studies following hematopoietic stem cell transplantation. *Eur J Oncol Nurs*. 2014;18(2):175-82.
30. Shang J, Wenzel J, Krumm S, Griffith K, and Stewart K. Who will drop out and who will drop in, exercise adherence in a randomized clinical trial among patients receiving active cancer treatment. *Cancer Nurs*. 2012;35(4):312-22.
31. Courneya KS, Friedenreich CM, Quinney HA, Fields AL, Jones LW, and Fairey AS. Predictors of adherence and contamination in a randomized trial of exercise in colorectal cancer survivors. *Psychooncology*. 2004;13(12):857-66.
32. Mock V, Frangakis C, Davidson NE, Ropka ME, Pickett M, Poniatowski B, Stewart KJ, Cameron L, Zawacki K, Podewils LJ, Cohen G, and McCorkle R. Exercise manages fatigue during breast cancer treatment: a randomized controlled trial. *Psychooncology*. 2005;14(6):464-77.
33. Copelan EA. Hematopoietic stem-cell transplantation. *N Engl J Med*. 2006;354(17):1813-26.
34. Passweg JR, Baldomero H, Bregni M, Cesaro S, Dreger P, Duarte RF, Falkenburg JH, Kroger N, Farge-Bancel D, Bobby Gaspar H, Marsh J, Mohty M, Peters C, Sureda A, Velardi A, Ruiz de Elvira C, and Madrigal A. Hematopoietic SCT in Europe: data and trends in 2011. *Bone Marrow Transplant*. 2013;48(9):1161-7.
35. Krebs in Deutschland 2009/2010. 9. Ausgabe. (Hrsg)., Robert Koch-Institut und die Gesellschaft der epidemiologischen Krebsregister in Deutschland e.V. Berlin, 2013.
36. Barrett AJ, and 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.

37. Gooley TA, Chien JW, Pergam SA, Hingorani S, Sorror ML, Boeckh M, Martin PJ, Sandmaier BM, Marr KA, Appelbaum FR, Storb R, and McDonald GB. Reduced mortality after allogeneic hematopoietic-cell transplantation. *N Engl J Med*. 2010;363(22):2091-101.
38. Ferrara JL, Levine JE, Reddy P, and Holler E. Graft-versus-host disease. *Lancet*. 2009;373(9674):1550-61.
39. Morishita S, Kaida K, Tanaka T, Itani Y, Ikegame K, Okada M, Ishii S, Kodama N, Ogawa H, and Domen K. Prevalence of sarcopenia and relevance of body composition, physiological function, fatigue, and health-related quality of life in patients before allogeneic hematopoietic stem cell transplantation. *Support Care Cancer*. 2012;20(12):3161-8.
40. White AC, Terrin N, Miller KB, and Ryan HF. Impaired respiratory and skeletal muscle strength in patients prior to hematopoietic stem-cell transplantation. *Chest*. 2005;128(1):145-52.
41. Morishita S, Kaida K, Ikegame K, Yoshihara S, Taniguchi K, Okada M, Kodama N, Ogawa H, and Domen K. Impaired physiological function and health-related QOL in patients before hematopoietic stem-cell transplantation. *Support Care Cancer*. 2012;20(4):821-9.
42. Christensen JF, Jones LW, Andersen JL, Daugaard G, Rorth M, and Hojman P. Muscle dysfunction in cancer patients. *Ann Oncol*. 2014;25(5):947-58.
43. Donohoe CL, Ryan AM, and Reynolds JV. Cancer cachexia: mechanisms and clinical implications. *Gastroenterol Res Pract*. 2011;2011:601434.
44. Muscaritoli M, Bossola M, Aversa Z, Bellantone R, and Fanelli F. Prevention and treatment of cancer cachexia: New insights into an old problem. *Europ Jur of Cancer*. 2006;42:31-41.
45. Larsen J, Nordstrom G, Ljungman P, and Gardulf A. Symptom occurrence, symptom intensity, and symptom distress in patients undergoing high-dose chemotherapy with stem-cell transplantation. *Cancer Nurs*. 2004;27(1):55-64.
46. Cyarto EV, Brown WJ, and Marshall AL. Retention, adherence and compliance: important considerations for home- and group-based resistance training programs for older adults. *J Sci Med Sport*. 2006;9(5):402-12.
47. Linhares YP, Pavletic S, and Gale RP. Chronic GVHD: Where are we? Where do we want to be? Will immunomodulatory drugs help? *Bone Marrow Transplant*. 2013;48(2):203-9.
48. Mitchell SA, Leidy NK, Mooney KH, Dudley WN, Beck SL, LaStayo PC, Cowen EW, Palit P, Comis LE, Krumlauf MC, Avila DN, Atlam N, Fowler DH, and Pavletic SZ. Determinants of functional performance in long-term survivors of allogeneic hematopoietic stem cell transplantation with chronic graft-versus-host disease (cGVHD). *Bone Marrow Transplant*. 2010;45(4):762-9.
49. Fraser CJ, Bhatia S, Ness K, Carter A, Francisco L, Arora M, Parker P, Forman S, Weisdorf D, Gurney JG, and Baker KS. Impact of chronic graft-versus-host disease on the health status of hematopoietic cell transplantation survivors: a report from the Bone Marrow Transplant Survivor Study. *Blood*. 2006;108(8):2867-73.
50. Lee HJ, Oran B, Saliba RM, Couriel DM, Shin K, Massey P, Neumann J, de Lima M, Champlin R, and Giralt S. Steroid myopathy in patients with acute graft-versus-host disease treated with high-dose steroid therapy. *Bone Marrow Transplant*. 2006;38(4):299-303.
51. Menconi M, Fareed M, O'Neal P, Poylin V, Wei W, and Hasselgren PO. Role of glucocorticoids in the molecular regulation of muscle wasting. *Crit Care Med*. 2007;35(9 Suppl):S602-8.
52. Morishita S, Kaida K, Yamauchi S, Sota K, Ishii S, Ikegame K, Kodama N, Ogawa H, and Domen K. Relationship between corticosteroid dose and declines in physical function among allogeneic hematopoietic stem cell transplantation patients. *Support Care Cancer*. 2013;21(8):2161-9.
53. Kortebein P, Ferrando A, Lombeida J, Wolfe R, and Evans WJ. Effect of 10 days of bed rest on skeletal muscle in healthy older adults. *JAMA*. 2007;297(16):1772-4.

54. Mosher CE, DuHamel KN, Rini C, Corner G, Lam J, and Redd WH. Quality of life concerns and depression among hematopoietic stem cell transplant survivors. *Support Care Cancer*. 2011;19(9):1357-65.
55. Mosher CE, Redd WH, Rini CM, Burkhalter JE, and DuHamel KN. Physical, psychological, and social sequelae following hematopoietic stem cell transplantation: a review of the literature. *Psychooncology*. 2009;18(2):113-27.
56. Pidala J, Anasetti C, and Jim H. Health-related quality of life following haematopoietic cell transplantation: patient education, evaluation and intervention. *Br J Haematol*. 2009;148(3):373-85.
57. Tichelli A, Rovo A, and Gratwohl A. Late pulmonary, cardiovascular, and renal complications after hematopoietic stem cell transplantation and recommended screening practices. *Hematology Am Soc Hematol Educ Program*. 2008:125-33.
58. Baker KS, Armenian S, and Bhatia S. Long-term consequences of hematopoietic stem cell transplantation: current state of the science. *Biol Blood Marrow Transplant*. 2010;16(1 Suppl):S90-6.
59. Chow EJ, Mueller BA, Baker KS, Cushing-Haugen KL, Flowers ME, Martin PJ, Friedman DL, and Lee SJ. Cardiovascular hospitalizations and mortality among recipients of hematopoietic stem cell transplantation. *Ann Intern Med*. 2011;155(1):21-32.
60. Andrykowski MA, Bishop MM, Hahn EA, Cella DF, Beaumont JL, Brady MJ, Horowitz MM, Sobocinski KA, Rizzo JD, and Wingard JR. Long-term health-related quality of life, growth, and spiritual well-being after hematopoietic stem-cell transplantation. *J Clin Oncol*. 2005;23(3):599-608.
61. Warburton DE, Nicol CW, and Bredin SS. Health benefits of physical activity: the evidence. *CMAJ*. 2006;174(6):801-9.
62. Bellizzi KM, Rowland JH, Arora NK, Hamilton AS, Miller MF, and Aziz NM. Physical activity and quality of life in adult survivors of non-Hodgkin's lymphoma. *J Clin Oncol*. 2009;27(6):960-6.
63. Jones LW, Courneya KS, Vallance JK, Ladha AB, Mant MJ, Belch AR, Stewart DA, and Reiman T. Association between exercise and quality of life in multiple myeloma cancer survivors. *Support Care Cancer*. 2004;12(11):780-8.
64. Blanchard CM, Baker F, Denniston MM, Courneya KS, Hann DM, Gesme DH, Reding D, Flynn T, and Kennedy JS. Is absolute amount or change in exercise more associated with quality of life in adult cancer survivors? *Prev Med*. 2003;37(5):389-95.
65. Vallance JK, Courneya KS, Jones LW, and Reiman T. Differences in quality of life between non-Hodgkin's lymphoma survivors meeting and not meeting public health exercise guidelines. *Psychooncology*. 2005;14(11):979-91.
66. Dyrstad SM, Hansen BH, Holme I, and Anderssen SA. Comparison of self-report versus accelerometer-measured physical activity. *MSSE*. 2013:99-106.
67. Wiskemann J, and Huber G. Physical exercise as adjuvant therapy for patients undergoing hematopoietic stem cell transplantation. *Bone Marrow Transplant*. 2008;41(4):321-9.
68. Persoon S, Kersten MJ, van der Weiden K, Buffart LM, Nollet F, Brug J, and Chinapaw MJ. Effects of exercise in patients treated with stem cell transplantation for a hematologic malignancy: a systematic review and meta-analysis. *Cancer Treat Rev*. 2013;39(6):682-90.
69. Wolin KY, Ruiz JR, Tuchman H, and Lucia A. Exercise in adult and pediatric hematological cancer survivors: an intervention review. *Leukemia*. 2010;24(6):1113-20.
70. Liu RD, Chinapaw MJ, Huijgens PC, and van Mechelen W. Physical exercise interventions in haematological cancer patients, feasible to conduct but effectiveness to be established: a systematic literature review. *Cancer Treat Rev*. 2009;35(2):185-92.
71. Wiskemann J, Nies R, and Vandenbergh D. Leukämien und Lymphome. In: F. Baumann, E. Jäger and W. Bloch editors. *Körperliche Aktivität und Sport bei Krebs*. Heidelberg: Springer; 2012, pp. 189-208.

72. van Haren IE, Timmerman H, Potting CM, Blijlevens NM, Staal JB, and Nijhuis-van der Sanden MW. Physical exercise for patients undergoing hematopoietic stem cell transplantation: systematic review and meta-analyses of randomized controlled trials. *Phys Ther*. 2013;93(4):514-28.
73. Jarden M, Baadsgaard MT, Hovgaard DJ, Boesen E, and 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.
74. Jarden M, Nelausen K, Hovgaard D, Boesen E, and Adamsen L. The effect of a multimodal intervention on treatment-related symptoms in patients undergoing hematopoietic stem cell transplantation: a randomized controlled trial. *J Pain Symptom Manage*. 2009;38(2):174-90.
75. Mello M, Tanaka C, and Dulley FL. Effects of an exercise program on muscle performance in patients undergoing allogeneic bone marrow transplantation. *Bone Marrow Transplant*. 2003;32(7):723-8.
76. Knols RH, de Bruin ED, Uebelhart D, Aufdemkampe G, Schanz U, Stenner-Liewen F, Hitz F, Taverna C, and Aaronson NK. 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.
77. Wiskemann J, Dreger P, Schwerdtfeger R, Bondong A, Huber G, Kleindienst N, Ulrich CM, and Bohus M. Effects of a partly self-administered exercise program before, during, and after allogeneic stem cell transplantation. *Blood*. 2011;117(9):2604-13.
78. Wiskemann J, Kleindienst N, Kuehl R, Dreger P, Schwerdtfeger R, and Bohus M. Effects of physical exercise on survival after allogeneic stem cell transplantation. *International Journal of Cancer*. 2015.

1.4 Outline

Results of previous studies in the context of HCT have been heterogeneous due to different modalities of exercise interventions as well as differences in treatment and evaluated time points. Furthermore, detailed information about adherence and contamination and their determinants are lacking. Consequently, there is insufficient evidence regarding the optimal exercise prescription, including intensity needed and individual response. The ultimate aim should be to develop personalized exercise prescriptions on the basis of current fitness status, time during treatment (PEACE framework), needs and preferences. This thesis will contribute to the indicated research gaps exploring the following aspects:

Firstly, physical performance and PRO data of the experimental group of our first RCT will be examined further in order to give answer if the initial performance level mediates effects of exercise response (Chapter 2).

Secondly, the design and the rationale of the PETRA study will be described in detail, to give background information about the data basis (Chapter 3).

Thirdly, the widely used ACSM intensity classification for endurance training prescription will be compared to values obtained in PETRA patients during cardiopulmonary exercise tests in order to give more precise exercise intensity recommendations in hematological cancer patients during and after treatment (Chapter 4).

And finally, recruitment, adherence and contamination of the first 153 patients in the PETRA study will be described and determinants for both, adherence and contamination will be presented in order to enhance future program design and data interpretation (Chapter 5).

Chapter 6 will give a short summary of all manuscripts and will discuss the findings in the light of the current literature and methodological aspects. This chapter ends with conclusion remarks and future perspective.

2 Manuscript I

Published in Bone Marrow Transplantation (BMT) 2014
Issue: 49
Pages: 443-448
Impact Factor: 3.46 (2013)
Submitted: 22 June 2013
Revised: 12 October 2013
Accepted for publication: 17 October 2013
Published online: 9 December 2013

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

J Wiskemann[1,2,3], R Kuehl[2], P Dreger[4]; R Schwerdtfeger[4], G Huber[6], CM Ulrich[2,7], D Jaeger [1], M Bohus[3]

[1]National Center for Tumor Diseases (NCT) and University Clinic Heidelberg, Germany
[2]National Center for Tumor Diseases (NCT) and German Cancer Research Center, Heidelberg, Germany
[3]Central Institute of Mental Health, Mannheim, Germany
[4]Department of Medicine V, University of Heidelberg, Heidelberg, Germany
[5]German Clinic for Diagnostic, BMT Unit, Wiesbaden, Germany
[6]Institute of Sports and Sport Science, University of Heidelberg, Germany
[7]Fred Hutchinson Cancer Research Centre, Seattle, United States

ABSTRACT

Patients undergoing allogeneic stem cell transplantation (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. In order 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 then fit patients. This result is of major clinical relevance and should encourage hematologists to promote exercise even more in impaired/unfit allo-HCT patients.

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

INTRODUCTION

Allogeneic stem cell transplantation (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 e.g. infections, graft-versus-host disease (GvHD), and transplant-related mortality rate is considerable [1]. Prior to 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, 6 new RCTs 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 of 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 an initial fit and unfit group, 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 RCT 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.

PATIENTS AND METHODS

Design

Our study was a prospective, multicenter randomized controlled trial (RCT) 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 prior to hospital admission. After admission, they continued training at the hospital. In this phase, the exercise training was supervised 2x/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 (3-5x/week endurance, 2x/week resistance training). A single session lasted 20 to 40 minutes. 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 platelet counts below 10.000/µl, signs of bleeding, hemoglobin level below 8g/dl, infections with fever >38ºC, 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 (e.g. telephone calls, 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 prior to admission, t_1 at the day of admission, t_2 at the day of discharge and t_3 6-8 weeks after discharge.

Maximal voluntary isometric strength (MVIS) was measured in Newton [N] by a hand-held-dynamometer (HHD; company: C.I.T. Technics; Netherlands). HHDs 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 seconds. Each measurement was repeated three times. Values <10% different from the median were excluded.

Endurance performance was measured by the six-minute walk test (6MWT) [19,20]. The 6MWT is a sub-maximal performance test which reflects the tasks of daily living and has been previously used in hematological cancer populations [3,9]. Patients were advised to walk back and forth down a hallway as fast as possible for six minutes. The six-minute 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 patients-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 (ANCOVA). The significant level was set at α <0.05. All statistical analyses were performed using SPSS (German Version 19.0 for Windows).

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].

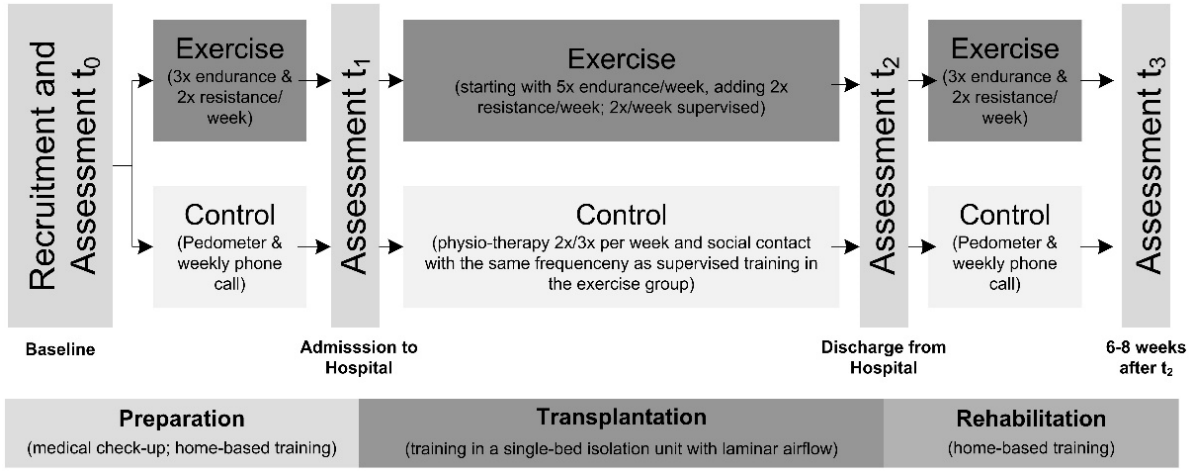

Figure 1. Study Design (with permission from the journal Blood)

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 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, 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. 27.3% of the EX *fit*, 17.2% of the EX *unfit* and 30.8% of the controls reported cardiologic co-morbidities (e.g. hypertension, 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 e.g. 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 to *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 ANCOVA 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.

Table 1. Baseline medical and demographic characteristic

	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 exact tes. [b]Wilcoxon test.

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)*
EX unfit n=28	257 (93)	293 (149)	234 (104)	235 (92)	-1.7%		Group (*P* =0.47) Age (*P* =0.24)
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)
EX unfit n=10	128 (35)	162 (63)	153 (70)	135 (47)	10.3		Group (*P* =0.17) Age (*P* =0.44)
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)
EX unfit n=10	124 (29)	140 (51)	130 (35)	128 (41)	3.4		Group (*P* =0.34) Age (*P* =0.37)
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)
EX unfit n=15	172 (33)	187 (54)	161 (40)	164 (42)	-4.4		Group (*P* =0.37) Age (*P* =0.41)
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)*
EX unfit n=11	501 (102)	535 (102)	482 (98)	553 (63)	13.4		Group (*P* =0.34) Age (*P* =0.30)

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

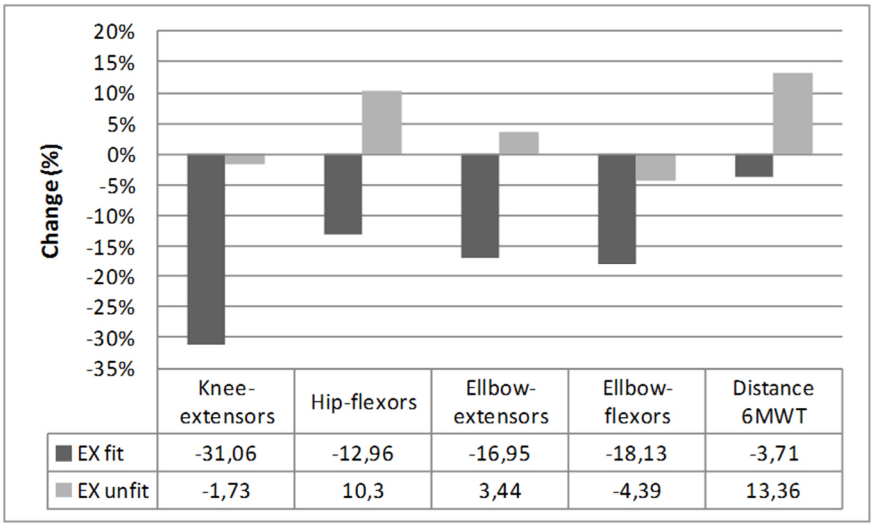

Figure 2. Baseline-stratified changes for different muscle groups and 6-min walk distance in initially *fit* and *unfit* patients. EX fit = initially fit patients in the exercise group; EX unfit = initially unfit patients in the exercise group.

Training response compared to 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.

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.

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 prior to transplantation, we demonstrate that the training response to the partly-supervised exercise intervention was superior in *unfit* patients compared to *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 physical fitness in the context of an intensive medical treatment, such as 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] showed also 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 nonmyeloablative 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.

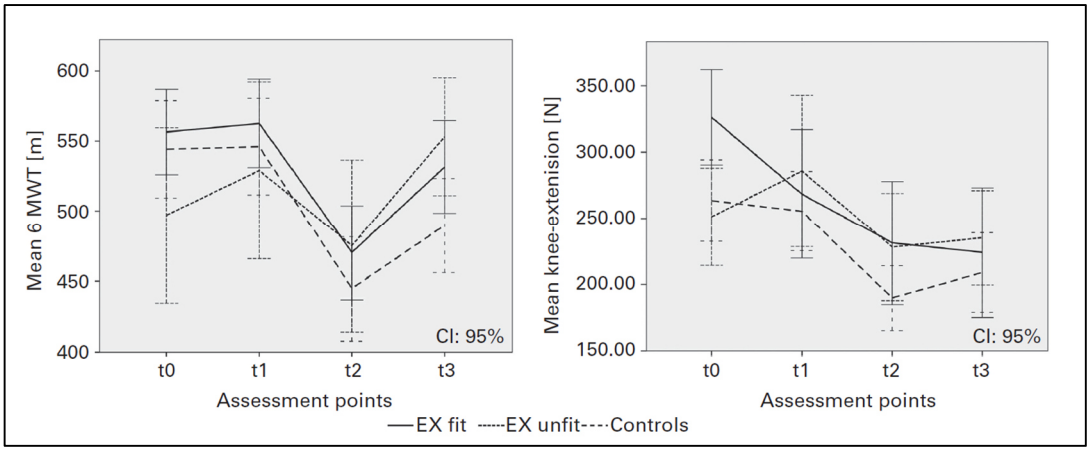

Figure 3: Development of 6-min walk distance (left) and knee-extension muscle strength (right) for initially fit and unfit exercising patients and for controls. EX fit = initially fit patients in the exercise group; EX unfit = initially unfit patients in the exercise group.

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 entireintervention 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 to a non-exercising control group, even if they have comparable age and gender-specific levels of physical fitness prior to the transplantation process.

Beside the "inappropriate intensity explanation" there are several reasons which 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 (e.g. bicycle ergometers, treadmill, and free weights) during the inpatient setting. Finally, controls also received physiotherapy regularly during their inpatient stay.

Our study had several strengths. It was one of the largest RCTs in the field of allo-HCT. Due to our large sample size, it was possible to perform a sub-group 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* 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 as *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 in order to preclude a fitness bias in statistical analyses of clinical exercise trials.

CONFLICT OF INTERESTS

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).

REFERENCES

1 Copelan EA. Hematopoietic stem-cell transplantation. *N Engl J Med* 2006; **354**: 1813-1826.

2 Morishita S, Kaida K, Ikegame K, Yoshihara S, Taniguchi K, Okada M *et al.* Impaired physiological function and health-related QOL in patients before hematopoietic stem-cell transplantation. *Support Care Cancer* 2012; **20**: 821-829.

3 White AC, Terrin N, Miller KB, Ryan HF. Impaired respiratory and skeletal muscle strength in patients prior to hematopoietic stem-cell transplantation. *Chest* 2005; **128**: 145-152.

4 Mosher CE, Redd WH, Rini CM, Burkhalter JE, DuHamel KN. Physical, psychological, and social sequelae following hematopoietic stem cell transplantation: a review of the literature. *Psychooncology* 2009; **18**: 113-127.

5 Mitchell SA, Leidy NK, Mooney KH, Dudley WN, Beck SL, LaStayo PC *et al.* Determinants of functional performance in long-term survivors of allogeneic hematopoietic stem cell transplantation with chronic graft-versus-host disease (cGVHD). *Bone Marrow Transplant* 2010; **45**: 762-769.

6 Schmitz KH, Courneya KS, Matthews C, Demark-Wahnefried W, Galvao DA, Pinto BM *et al.* American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. *Med Sci Sports Exerc* 2010; **42**: 1409-1426.

7 Wiskemann J, Huber G. Physical exercise as adjuvant therapy for patients undergoing hematopoietic stem cell transplantation. *Bone Marrow Transplant* 2008; **41**: 321-329.

8 Coleman EA, Coon SK, Kennedy RL, Lockhart KD, Stewart CB, Anaissie EJ *et al.* Effects of exercise in combination with epoetin alfa during high-dose chemotherapy and autologous peripheral blood stem cell transplantation for multiple myeloma. *Oncol Nurs Forum* 2008; **35**: E53-61.

9 Shelton ML, Lee JQ, Morris GS, Massey PR, Kendall DG, Munsell MF *et al.* A randomized control trial of a supervised versus a self-directed exercise program for allogeneic stem cell transplant patients. *Psychooncology* 2008; **18**: 353-359.

10 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**: 725-737.

11 Hacker ED, Larson J, Kujath A, Peace D, Rondelli D, Gaston L. Strength training following hematopoietic stem cell transplantation. *Cancer Nurs* 2011; **34**: 238-249.

12 Knols RH, de Bruin ED, Shirato K, Uebelhart D, Aaronson NK. Physical activity interventions to improve daily walking activity in cancer survivors. *BMC Cancer* 2010; **10**: 406.

13 Wiskemann J, Dreger P, Schwerdtfeger R, Bondong A, Huber G, Kleindienst N *et al.* Effects of a partly self-administered exercise program before, during, and after allogeneic stem cell transplantation. *Blood* 2011; **117**: 2604-2613.

14 Skinner JS, Jaskolski A, Jaskolska A, Krasnoff J, Gagnon J, Leon AS *et al.* Age, sex, race, initial fitness, and response to training: the HERITAGE Family Study. *J Appl Physiol* 2001; **90**: 1770-1776.

15 Gruber W, Orenstein DM, Braumann KM. Do responses to exercise training in cystic fibrosis depend on initial fitness level? *Eur Respir J* 2011; **38**: 1336-1342.

16 Knols RH, Aufdemkampe G, de Bruin ED, Uebelhart D, Aaronson NK. Hand-held dynamometry in patients with haematological malignancies: measurement error in the clinical assessment of knee extension strength. *BMC Musculoskelet Disord* 2009; **10**: 31.

17 Mello M, Tanaka C, Dulley FL. Effects of an exercise program on muscle performance in patients undergoing allogeneic bone marrow transplantation. *Bone Marrow Transplant* 2003; **32**: 723-728.

18 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**: 26-32.

19 Enright PL. The six-minute walk test. *Respir Care* 2003; **48**: 783-785.

20 Crapo R, Casaburi R, Coaties A, Enright P, MacIntyre N, McKay P *et al.* ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med* 2002; **166**: 111-117.

21 Smets EM, Garssen B, Bonke B, de Haes JC. The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. *J.Psychosom.Res.* 1995; **39**: 315-325.

22 Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ *et al.* The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J.Natl.Cancer Inst.* 1993; **85**: 365-376.

23 Holland JC, Andersen B, Breitbart WS, Dabrowski M, Dudley MM, Fleishman S *et al.* Distress management. *J.Natl.Compr.Canc.Netw.* 2007; **5**: 66-98.

24 Enright PL, Sherrill DL. Reference equations for the six-minute walk in healthy adults. *Am J Respir Crit Care Med* 1998; **158**: 1384-1387.

25 Baumann FT, Zopf EM, Nykamp E, Kraut L, Schule K, Elter T *et al.* Physical activity for patients undergoing an allogeneic hematopoietic stem cell transplantation: benefits of a moderate exercise intervention. *Eur J Haematol* 2011; **87**: 148-156.

26 DeFor TE, Burns LJ, Gold EM, Weisdorf DJ. A randomized trial of the effect of a walking regimen on

the functional status of 100 adult allogeneic donor hematopoietic cell transplant patients. *Biol.Blood Marrow Transplant.* 2007; **13**: 948-955.

27 Vallance JK, Courneya KS, Plotnikoff RC, Yasui Y, Mackey JR. Randomized controlled trial of the effects of print materials and step pedometers on physical activity and quality of life in breast cancer survivors. *J Clin Oncol* 2007; **25**: 2352-2359.

28 Majhail NS, Rizzo JD, Lee SJ, Aljurf M, Atsuta Y, Bonfim C *et al.* Recommended screening and preventive practices for long-term survivors after hematopoietic cell transplantation. *Bone Marrow Transplant* 2012; **47**: 337-341.

29 De Lisio M, Baker JM, Parise G. Exercise promotes bone marrow cell survival and recipient reconstitution post-bone marrow transplantation, which is associated with increased survival. *Experimental hematology* 2013; **41**: 143-154.

30 Weiss BM, Vogl DT, Berger NA, Stadtmauer EA, Lazarus HM. Trimming the fat: obesity and hematopoietic cell transplantation. *Bone Marrow Transplant* 2013; **48**: 1152-1160.

31 Urbain P, Birlinger J, Lambert C, Finke J, Bertz H, Biesalski HK. Longitudinal follow-up of nutritional status and its influencing factors in adults undergoing allogeneic hematopoietic cell transplantation. *Bone Marrow Transplant* 2013; **48**: 446-451.

3 Manuscript II

Submitted to BMC Cancer
Impact Factor: 3.32 (2013)
Submitted: 22. June 2015

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

Wiskemann, Joachim[1,2,3 *] ; Kuehl, Rea[1,2 *]; Dreger, Peter[4]; Huber, Gerhard[6]; Kleindienst, Nikolaus[3]; Ulrich, Cornelia M.[7]; Bohus, Martin[3,8]

[1]National Center for Tumor Diseases (NCT) and Heidelberg University Hospital, Germany
[2]National Center for Tumor Diseases (NCT) and German Cancer Research Center, Heidelberg, Germany
[3]Central Institute of Mental Health, Mannheim, Germany
[4]Department of Medicine V, Heidelberg University, Heidelberg, Germany
[6]Institute of Sports and Sport Science, Heidelberg University, Germany
[7]Huntsman Cancer Institute, Utah, United States
[8] Faculty of Health, University of Antwerp, Belgium

* shared first authors

ABSTRACT

Background: Allogeneic stem cell transplantation (allo-HCT) is associated with high treatment-related mortality and innumerable physical and psychosocial complications and side-effects, such as high fatigue levels, loss of physical performance, infections, graft-versus-host disease (GvHD) and distress. This leads to a reduced quality of life, not only during and after transplantation, but also in the long term. Exercise interventions have been shown to be beneficial in allo-HCT patients. However, to date, no study has focused on long-term effects and survival. Previous exercise studies used 'usual care' control groups, leaving it unclear to what extent the observed effects are based on the physical effects of exercise itself, or rather on psychosocial factors such as personal attention. Furthermore, effects of exercise on and severity of GvHD have not been examined so far. We therefore aim to investigate the effects and biological mechanisms of exercise on side-effects, complications and survival in allo-HCT patients during and after transplantation.

Methods/Design: The PETRA study is a randomized, controlled intervention trial investigating the effects of a yearlong partly supervised mixed exercise intervention (endurance and resistance exercises, 3-5 times per week) in 256 patients during and after allogeneic stem cell transplantation. Patients in the control group perform

progressive muscle relaxation training (Jacobsen method) with the same frequency. Main inclusion criterion is planned allo-HCT. Main exclusion criteria are increased fracture risk, no walking capability or severe cardiorespiratory problems. Primary endpoint is overall survival after two years; secondary endpoints are non-relapse mortality, median survival, patient reported outcomes including cancer related fatigue and quality of life, physical performance, body composition, haematological/immunological reconstitution, inflammatory parameters, severity of complications and side-effects (e.g. GvHD and infections), and cognitive capacity.

Discussion: The PETRA study will contribute to a better understanding of the physiological and psychological effects of exercise training and their biological mechanisms in cancer patients after allo-HCT. The ultimate goal is the implementation of optimized intervention programs to reduce side-effects and improve quality of life and potentially prognosis after allogeneic stem cell transplantation.

Trial registration: ClinicalTrials.gov Identifier: NCT01374399

Keywords: Exercise, stem cell transplantation, prognosis, survival, cancer, mechanisms, fatigue, side-effects, mortality, hematological malignancies

BACKGROUND

Allogeneic stem cell transplantation (allo-HCT) is the only curative medical treatment option for patients with haematological malignancies in high-risk situations e.g. acute leukaemia. However, patients suffer from numerous treatment related side-effects and complications, and the transplant-related mortality is high [1]. Exercise constitutes a potentially promising intervention approach for this patient group. Over the last years, several clinical trials have contributed to the growing body of evidence showing the beneficial effects of exercise in cancer patients [2-5], and some general exercise recommendations for cancer patients have already been published [6] also in the field of allo-HCT [7].

Our group has reviewed exercise intervention studies in the context of stem cell transplantation and illustrated that exercise interventions at different time points during and after HCT might significantly improve physical performance, quality of life, symptom control and fatigue [7]. Since publication of this review, 6 new randomized controlled trials (RCTs) have been published supporting the findings [8-13]. These studies were included in a recent review and meta-analysis by Persoon et al. [14] and the authors found that exercise significantly improved cardiorespiratory fitness, lower extremity muscle strength and fatigue and had also a small effect on upper extremity muscle strength, quality of life (QoL), physical, emotional and cognitive function. The researcher concluded that more high-quality studies were needed [14]. However, it is still not possible to give patients clear advice regarding the best type, intensity, start and duration of an exercise program.

Prior to allo-HCT, patients' physical performance is already affected due to the disease itself and/or previous treatment [15, 16]. Furthermore, emerging evidence indicates that cancer patients have considerably impaired cardiorespiratory fitness as a result of the toxic effects of anticancer therapy or as a consequence of the disease (for example cachexia, deconditioning, anaemia) [17]. Thus, physical activity levels have been described as generally low in a group of haematological cancer survivors [18]. Furthermore, one study compared the quality of life of 662 HCT survivors with age- and sex-matched healthy controls and observed poorer general health, physical function, well-being, depression, cognitive function, and fatigue in HCT survivors [19]. A major complication after allo-HCT is graft-versus-host disease (GvHD). GvHD is the leading cause of morbidity and high transplant-related mortality. It is characterized by a reaction of donor T-cells against patient tissues e.g. mucosa or skin [1, 20]. Moreover, chronic GvHD is associated with a lower physical performance and functional capacity [21]. A recent review shows that patients after HCT are likely to have long-term difficulties with physical functioning, problems with fatigue, distress and a deteriorated psychological well-being [22]. Furthermore, patients after allo-HCT are at increased risks of cardiovascular events and pulmonary complications [23, 24].

Moreover, fatigue is a frequently reported adverse side-effect in cancer patients [25]. One study described the fatigue experience in allo-HCT patients during the first 100 days. In this observation, 68% reported fatigue at the day of transplantation, 90% at day 30 and 81% at day 100 after allo-HCT [26]. A Cochrane review and an American College of Sports Medicine (ACSM) roundtable concluded that exercise may be an effective treatment against fatigue [2, 6]. Our recently published RCT supports these finding by demonstrating positive effects of exercise during and after allo-HCT on fatigue [13]. Mechanisms underlying the positive effect of exercise on fatigue are not fully elucidated, current models favor physiological and biological effects, for example enhanced physical performance, reduced inflammation, and less distress [27, 28].

A recent Cochrane review aimed to evaluate the effects of aerobic exercise in haematological

malignancies. Exercise improved quality of life, especially physical functioning, depression and fatigue. The authors emphasised that none of the included studies investigated effects on survival. They concluded that trials with overall survival as primary endpoint are needed [29]. So far, the evidence regarding a possible influence of exercise on survival after cancer diagnosis is limited. A recent review by Ballard-Barbash et al. (2012) found consistent evidence from 27 observational studies, that physical activity is associated with reduced all-cause, breast-cancer and colon-cancer specific mortality, but evidence regarding other cancers is currently insufficient [30]. Studies suggest that cardio-respiratory fitness may be a robust predictor of prognosis in non-small lung cancer patients and metastatic breast cancer [17, 31]. Courneya et al. (2014) presented for the first time data from a RCT in 242 breast cancer patients, and found a non-significant trend for a better outcome (overall survival and disease-free survival) in the exercise group [32]. In addition, a small cohort study with 22 patients showed that patients with low cardiorespiratory fitness before allo-HCT had a higher risk of mortality after allo-HCT [33], furthermore, in a prospective cohort study in allo-HCT patients, the Karnofsky Performance Score (KPS) was an independent predictor of survival, and KPS <90% was a predictor of non-relapse mortality (NRM) [34].

Data from our RCT in allo-HCT patients [13] also suggest a potential effect of exercise on survival. We observed a significantly reduced two-year total mortality (TM) for the experimental group (12% vs. 28%, p=.034) after inpatient period. The effect was controlled for major confounding factors (Gratwohl Score, KPS, conditioning regime, gender, and fitness prior transplantation). Similar results were observed for non-relapse mortality (4% vs. 13%, p=.017) when controlled for potential confounders. When we included the inpatient period, the risk reductions were similar but not significantly different. Interestingly, fitness at baseline was protective against NRM (p>.001). These results are encouraging, however, a major limitation of this study is that this was a post-hoc analysis and the study was not powered for the primary endpoint survival [35].

In consequence of the above mentioned findings, we currently perform an RCT to investigate the effects and biological mechanisms of a partly supervised yearlong exercise training on prognosis, complications, side-effects and biomarkers in patients during and after allo-HCT. To determine the specific effect of the exercise intervention itself beyond potential psychosocial effects, patients in the control group receive a comparable training schedule but with muscle relaxation according to the Jacobsen method, and the same personal attention as the exercise group.

METHODS/DESIGN

Study design

The PETRA study (acronym for Physical Exercise Training versus Relaxation in Allogeneic stem cell transplantation) is a 12-month prospective, randomized, controlled clinical intervention trial in patients during and after allogeneic stem cell transplantation. Patients have to provide written informed consent prior to participation in the study. After baseline assessments, participants are randomized to a mixed type exercise program (resistance and endurance exercises) or a relaxation program over a period of one year. Both interventions are administered partly supervised. Endpoints are assessed before admission to hospital (baseline, t0), at the day of discharge (t1), day 100 after transplantation (t2), and day 180, 270 and 365 post transplantation (t3, t4, t5). Follow-up measurement will be 720 days after transplantation. [see Figure 1].

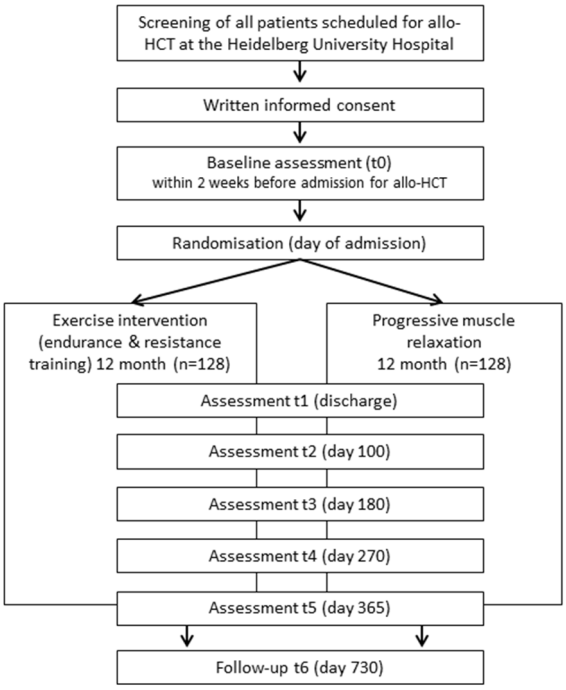

Figure 1: CONSORT: Study Flow of the PETRA study

The PETRA study has been approved by the ethic committees of the Ethic Committee II of the University of Mannheim (number 2009-349N-MA) and Heidelberg University (number S-021/2011) and is registered at ClinicalTrials.gov (NCT01374399).

Objectives

The primary objective of PETRA is to determine the effect of exercise on 2-year overall- survival after allo-HCT.

Secondary objectives are to estimate the effect of exercise on 2-year non-relapse mortality, median survival, fatigue, quality of life, physical fitness, including muscle strength, cardio-respiratory fitness, and body composition as well as on cognitive function. The effects of exercise on immunologic and inflammatory parameters and factors relevant for cancer prognosis and GvHD will be investigated and compared to the progressive muscle relaxation group. Finally, the sustainability of the effects will be assessed 720 days after allo-HCT.

Outcome Measures

The outcome measures used in the PETRA study are summarized in Table 1.

Primary Outcome

Two-year overall survival data will be collected using medical logs and will be approved by the study physician (PD).

Secondary Outcomes

Non-relapse mortality and median survival

We will distinguish between 2-year non-relapse mortality (e.g. related to GvHD, sepsis), median survival and median disease-free survival. Survival data will be collected using medical logs and will be approved by the study physician (PD).

Physical fitness

Muscle strength is assessed by measuring isometric (4 positions) and isokinetic (1 angular velocity) maximal muscle capacity with the IsoMed 2000® diagnostic module (isokinetic evaluation and training machine). The protocol includes testing of representative muscle groups for lower (knee extensors and flexors, hip flexor and extensor) and upper (elbow flexor and extensor) extremity. Reliability and validity of isokinetic dynamometer machines have been reported in several studies [36-38]. Additionally, a hand-held-dynamometer (C.I.T. Technics) is applied to assess isometrically 6 different muscle groups within standardized test positions (knee-extensors, knee-flexors, hip-abductors, hip-flexors, elbow-flexors and elbow-extensors) [39]. Each measurement is repeated 3 times, values that are <10% different from the median will be excluded. Hand-held–dynamometers were already applied in hematological cancer patients [13, 40, 41].

Endurance performance (maximum oxygen uptake, VO2peak) is measured by performing a symptom-limited maximal cardiopulmonary exercise test (CPET) with a step protocol (starting at 50 watts with steps of 25 watts every 2 minutes) on a bicycle ergometer. The criteria of exhaustion is defined as achieved estimated maximum heart rate, and respiratory exchange ratio >1.1. VO2peak is defined as highest 30-second average during the test. Peak workload, peak oxygen uptake and oxygen uptake and workload at ventilatory threshold will be taken for analysis. Cardiorespiratory exercise testing is well established in cancer patients and recommendations for testing procedures as well as safety guidelines in clinical trials with cancer populations exist [42-44]. Furthermore, the six-minute walk test is applied to measure submaximal endurance performance. Heat rate and O2-saturation is assessed before, during and after the test and the individual perceived exhaustion is measured using the RPE-Scale. [45] For reference values the formula by Enright et al. (1998) will be used [46]. The six-minute walk test was already applied in hematological cancer patients [8, 13].

Body composition of the participants is estimated with bioelectrical impedance analysis (BIA). This non-invasive method determines the electrical impedance, or opposition to the flow of an electric current through body tissues to calculate an estimate of total body water, fat-free body mass and body fat [47]. BIA gives reliable measurements of body composition with minimal intra- and inter-observed variability [48]. In addition, body weight and height are measured.

Accelerometer (ActiGraph GT3X) is used to assess physical activity behavior. The ActiGraph is a triaxial accelerometer, that records motion in different planes and provides information about intensity, frequency and duration of physical activity [49]. Patients will wear the accelerometers during hospital stay for the transplantation and at all measurement points (except t1) for 10 days at home during daytime. Accelerometers were already used in HCT patients [50].

Quality of life (QoL)

QoL is assessed with the validated 30-item self-assessment questionnaire of the European Organisation for Research and Treatment of Cancer (EORTC QLQ-C30, version 3.0). It includes five multi-item functional scales (physical, role, emotional, cognitive, and social function), three multi-item symptom scales (fatigue, pain, nausea/vomiting) and six single items assessing further symptoms (dyspnea, insomnia, appetite loss, constipation, diarrhea) and financial difficulties [51]. In addition, the 29-item high-dose chemotherapy (EORTC QLQ-HDC-29) is applied, assessing common problems after stem cell transplantation, e.g. gastro-intestinal side-effects and worry/anxiety [52]. Scores will be derived according to the EORTC scoring manual. Reference values are available from the EORTC reference manual, a review, including

2,800 patients before and after HCT [53] and from a sample of the general German population stratified by gender and age [54]. Furthermore, evidence-based guidelines for the interpretation of the clinical relevance of changes in the different EORTC QLQ-C30 subscales were recently published [55], categorizing differences between scores in trivial, small, medium or large effect sizes.

Fatigue

Fatigue will be assessed with the Multidimensional Fatigue Inventory (MFI) which is a 20-item, multidimensional self-assessment questionnaire that has been validated for a German-speaking population [56]. It covers five different dimensions of fatigue (general fatigue, physical fatigue, reduced activity, reduced motivation and mental fatigue). Scores are derived by summing the answers (five-stage scale) of the appropriate items.

Table 1 Assessments and instruments used in the PETRA study

Outcomes	Instrument	t0	t1	t2	t3	t4	t5	t6
Primary endpoint								
Overall 2-year survival	Medical log (ongoing assessment)							
Secondary endpoints								
2-year non-relapse mortality, median (disease-free) survival	Medical log (ongoing assessment)							
Quality of life	EORTC QLQ30 / HDC-29 module	X	X	X	X	X	X	X
Fatigue	Multidimensional Fatigue Inventory (MFI)	X	X	X	X	X	X	X
Muscle strength	Isometric and isokinetic strength of representative muscle groups for upper and lower extremity measured at the IsoMed2000®	X			X		X	X
	Hand-Held-Dynamometer (isometric)	X	X	X	X	X	X	X
Cardiorespiratory fitness	CPET (VO_2peak)	X			X		X	X
	6-Minute Walk Test	X	X	X	X	X	X	X
Body composition	bioelectrical impedance analysis, weight, height	X	X	X	X	X	X	X
Physical Activity	Accelerometry	X		X	X	X	X	X
Depression	CES-D	X	X	X	X	X	X	X
Distress	NCCN-Distress	X	X	X	X	X	X	X
Locus of control	KKG (German)	X	X	X	X	X	X	X
Cognitive function	Trail-making-test	X	X	X	X	X	X	X
Common side-effects	VAS, every week, later every 3 weeks							
Biomarker	Various methods (ELISA)	X	X	X	X	X	X	X
Oxidative stress marker	Analysed in urine samples	X	X	X	X	X	X	X
Others								
Socio-demographic factors	Recording of date of birth, education, occupation, familial situation, smoking, alcohol consumption	X					X	X
Medical history	Recording of pre-existing diseases, therapies	X						
Treatment data	Conditioning, complications		X					
Karnofsky Performance Score	Physician rating	X	X	X	X	X	X	X
Medication (immunosuppression, corticosteroids, analgesics)	Recorded at each visit/phone call on a medication log form	X	X	X	X	X	X	X
Physical activity history	Physical activity in adolescence, pre-diagnosis, during, and after intervention is recorded, including walking, cycling, and sports activities	X			X		X	X

Reference values of the MFI scores are available from a representative sample of the German population including 2,037 subjects [57]. The use of the MFI is recommended in cancer patients [58].

Distress

Distress will be assessed with the Distress-Thermometer, developed from the National Comprehensive Cancer Network (NCCN) as a screening tool [59, 60]. The Distress-Thermometer has already been validated in stem cell transplantation patients [61].

Depression

Depressive symptoms are assessed with the 20-item Center for Epidemiological Studies Depression Scale (CES-D). The CES-D scale is a widely used validated self-report instrument to measure current depressive symptomatology and to identify possible cases of depressive disorders, both in the general population and in patients with cancer [62].

Locus of control

Locus of control is measured by a validated German 21-item questionnaire *Assessment of health and sickness locus of control* (KKG). It comprises 3 subscales, assessing internal, social external and fatalistic external locus of control. [63] The questionnaire is based on the Multidimensional Health Locus of Control Scale (MHLC) [64].

Cognitive function

The cognitive function (concentration, cognitive flexibility) is estimated using the trail-making-test. This is a standardized, reliable and valid measure used in neuropsychological diagnostics [65, 66]. The test measures the time needed by the participant to connect numbers and letters spread over a sheet of paper in a logical sequence.

Biomarkers

Serum and PBMCs are derived from whole peripheral blood samples, processed within 4 hours after taking the blood sample and stored at -80°C or cryopreserved in liquid nitrogen (PBMCs) for analyses of biomarkers. Urine samples are collected for analyses of biomarkers of oxidative stress, i.e. urinary F2-isoprostane and 8-oxo-dG measured by chromatography-based methodology. Blood samples are collected for analyses of biomarkers of GvHD, i.e. inflammatory (e.g. IL-1, IL-4, IL-10, TNF-α) and endothelial parameters (e.g. angiopoetin-2, thrombomodulin (sTM)) measured by ELISA.

Side-effects of cancer treatment

Severity and duration of GvHD will be recorded by attending physicians every week according to the classification by Thomas et al. [67]. Furthermore, during allo-HCT and up to day 100 after, common side effects like nausea, diarrhea, appetite loss, pain, fatigue, concentration difficulties and anxiety are assessed weekly during phone calls using a visual analogue scale. After day 100 until the end of intervention (day 365 after) patients are questioned on these parameters during every phone call (depending on clinical status every 2-4 weeks). Infections are documented via medical chart review.

Safety issues

Potential adverse events (AEs) and serious adverse events (SAEs) causally related to the intervention or assessment procedure will be recorded. Patients are informed about contraindications for exercise sessions (thrombopenia, bleeding, infections including fever, dizziness, strong nausea/ vomiting, and strong pain) and advised to stop exercising when they feel that symptoms get stronger.

Sample size

Sample size was chosen to achieve adequate statistical power ($1-\beta = 0.8$) for detecting a difference between the exercise and relaxation group with respect to two-year overall survival (primary outcome). The calculation is based on the two-year overall survival rates of our previous RCT (0.66 in the exercise group vs 0.49 in the control group) [35]. Accordingly, 128 participants per group (total number = 256) are needed to achieve adequate power to detect a significant (two-tailed $\alpha = 0.05$) difference from Kaplan-Meier estimates tested for equality by log-rank tests.

Participants and setting

All patients, scheduled for an allo-HCT at the Heidelberg University Clinic are invited to participate in the PETRA study. Inclusion criteria are age ≥18 years and the ability to understand and follow the study protocol. Exclusion criteria comprise contra-indications for progressive exercise training, i.e. inability to walk or stand, instable bone lesions, severe neurological deficiencies, severe cardiac or cardiovascular diseases and severe pulmonary global insufficiency.

Recruitment and randomization

All eligible patients scheduled for allo-HCT at the University Hospital in Heidelberg are briefly informed about the PETRA study during the preparation visit (about 2-3 weeks before admission for allo-HCT) by case-management. If interested, patients are then informed in detail by the PETRA study coordinator. Upon written informed consent, the patient is included in the trial and scheduled for baseline assessment (t0), which should be within 14 days prior to start of conditioning for allo-HCT.

After completion of the baseline assessments, the participant is randomly allocated to one of the two intervention groups. Allocation is done by the

minimization method [68] stratified by disease, age (< 40 / ≥ 40 years of age), gender, remission state (CR/ no CR), and intensity of conditioning (full/ doses reduced). Stratification is used in the randomization process, as we anticipate these variables to have major influence on the outcome.

Interventions

The training starts at the same day as the conditioning treatment. Both intervention programs are performed 3-5 times per week for 12 months. During the first phase (hospital stay for allo-HCT) participants perform the program 3 times under supervision and guidance of an experienced therapist, 2 times self-directed. During the second phase (after discharge), patients perform both interventions self-directed at home. Until assessment on day 100 weekly phone calls in both groups will allow for adaptation of the program and enhance motivation/ adherence, 3 training sessions per week are recommended. After day 100 assessment, phone calls will take place every 2-3 weeks.

Exercise Intervention

All patients receive an exercise manual with background information (including contraindications for training, motivation), instructions for tailoring the training intensity (depending on clinical status), descriptions for different resistance exercises for the whole body and endurance exercises. Patients receive stretch bands and free weights for resistance exercises, for endurance exercises patients have access to a stationary bicycle (patient room) and a treadmill (hallway) during the inpatient period. We developed a self-rating instrument which helps patients to find the appropriate exercise intensity (including RPE scale) [13]. The exercise intervention complies with the ACSM exercise guidelines for cancer survivors and healthy adults and is progressed on an individual basis [6, 69]. A complete resistance training session includes 6 to 10 exercises for major upper and lower muscle groups and is recommended 2-3 times per week. Endurance training comprises bicycling or walking/jogging 3 times per week. Patients are encouraged to increase exercise intensity when they reach 3 sets of 12 repetitions for the resistance exercises or when they feel less exhausted using the RPE-scale (target 12-14 for endurance exercise, 14-16 for resistance exercise) [70]. The exercise program is performed on a very individual basis and includes also some psychological aspects e.g. motivation, goal setting, dealing with barriers, and regular feedback on physical performance data is given to promote adherence. [71] Adherence to FITT components (frequency, intensity, type, timing) will be described [72] to ensure correct interpretation of the findings. Furthermore, it is possible to perform the training in an appropriate sport/ exercise facility close to patients' homes. Within the scope of the PETRA study we will also develop a network called *'OnkoActive'*, which will enable referral to specialized exercise facilities. Furthermore, within *'OnkoActive'* an internet-based training platform will be developed to support the home-based intervention.

Relaxation Intervention

The progressive muscle relaxation method according to Jacobsen does not include any aerobic or muscle strengthening components [73]. Patients receive a manual with background information, an audio CD with 2 different versions (long/ short version) and a portable CD player. Patients in the control group will receive the standard physiotherapy program and will also have access to a bicycle ergometer and treadmill during the inpatient period.

Data analysis

The main intervention effect will be assessed on the basis of a Cox-regression analysis between exercisers and controls (relaxation group) as defined at randomization, regardless of exercise adherence, i.e. according to the intent-to-treat principle.

The differences in secondary endpoints between groups will be assessed using mixed models, which accounts for repeated observations on the same subjects over time. This method provides a more efficient estimate of the intervention effect in pretest-post-test trials than traditional methods [74]. Mixed models will also be used for testing to which extent differences between the treatment groups depend on training adherence, changes in muscle strength, cardiorespiratory fitness, and body composition. Normality assumptions will be checked and, if deviation from normality is detected the data will be transformed accordingly.

In addition, change in physical activity behavior post intervention will be monitored on an explorative basis.

DISCUSSION

Treating hematological malignant diseases with allo-HCT is highly demanding for patients who experience numerous side-effects and face a very high risk of severe treatment related complications, such as GvHD and severe infections, both in the short and long-term. In general, survival rates after allo-HCT are relatively low.

Recently, our group demonstrated that there may be a positive effect of exercise on survival after allo-HCT. In our first RCT we observed a significant reduced total mortality for the experimental group (12% vs. 28%, p=.034) and for NRM (4% vs. 13%, p=.017). Furthermore, we observed that physical fitness prior transplantation was highly protective against NRM [35]. The cohort study by Wood et al.

also suggests an association between fitness level prior transplantation and risk of mortality [33], but a small sample size of 22 patients and no use of multivariate models hamper the interpretation of these results. Against this background we designed the PETRA study. PETRA will add to current knowledge on exercise in allo-HCT patients with respect to several aspects: (1) Effect of yearlong exercise intervention on prognosis; (2) exercise effect on side-effects and complications, e.g. physical performance, QoL, fatigue; (3) exercise effect on GvHD and hematological/immunological reconstitution; and (4) sustainability and long-term effects of exercise intervention.

Given the indication of reducing mortality in cancer survivors by an appropriate physical active lifestyle, the question about possible mechanisms occurs. Some evidence suggests several potential mechanisms underlying [30]. One discussed mechanism is inflammation [75]. Several trials reported that exercise can reduce C-reactive protein (CRP), which is a marker of chronic inflammation [76-78] and change Interleukin-6 (IL-6) levels. IL-6 produced by muscle fibers during and after exercise stimulates the circulation of anti-inflammatory cytokines, such as IL-1ra and IL-10 and inhibits the production of tumor necrosis factor alpha (TNF-α) [79]. In a prospective cohort study in breast cancer patients, elevated CRP and serum amyloid A were associated with reduced overall survival [80]. Furthermore, when exercise potentially can influence parts of the immune system, the question arises, if a GvHD reaction in allo-HCT patients can also be influenced by exercise. To our knowledge, no intervention study in humans investigated a possible association between exercise and severity of the major side-effect GVHD. New results from mice experiments suggest that physical exercise can have a positive impact on GvHD. The researchers showed that endurance training (5 times per week) in mice was beneficial with regard to overall survival and also alters GvHD symptom severity. Furthermore, the authors revealed possible pathways for altering GvHD by demonstrating that exercising mice had lower levels of anti-inflammatory cytokines (IL-4 and TNF-α) [81]. Based on these findings, we aim to investigate whether exercise is able to alter GvHD severity in human adults. We are further interested to elucidate other possible exercise pathways altering GvHD by investigation of endothelial markers. Markers of interest are blood biomarkers of inflammation and TNF-α as well as endothelial markers and hepatocyte growth factor [82-85]. Natural killer cells (NK-cells) have also been shown to modulate acute GvHD, infections and recurrence [86, 87]. The positive effect of exercise on NK-cell activity in cancer patients could already be shown in studies [88], and a review about NK-cells and exercise suggests exercise as an adjunct therapy to promote expansion of NK-cell subsets [89]. Interestingly, one RCT in allo-HCT patients could already observe a positive effect of exercise during transplantation process on lymphocyte count [90].

Additionally, restoring the function of the entire haematological system after allo-HCT is an important prognostic indicator [91, 92]. Therefore, we focus also on exercise effects on haematological recovery after allo-HCT. A potential positive effect on the haematological system e.g. lymphocytes, haemoglobin could already be shown [8, 90, 93].

A central secondary endpoint is cancer-related fatigue. Fatigue is described as the most distressing side effect in cancer treatment, however, the pathophysiology of fatigue and the possible positive effect of exercise on its prevention/therapy are not well understood [94]. Therefore, our trial enables investigation of the effects of exercise on immunologic parameters as well as on biomarkers of inflammation and oxidative stress as possible mediators of fatigue [95, 96]. However, not only fatigue is a common side-effect. As a consequence of longer periods of drug intake, e.g. immune suppression and antibiotics, patients often suffer from nausea, diarrhea and further complaints. Recent studies indicated a better symptom control in exercising patients [97].

Our decision of choosing an intervention period of one year was based on the consideration that the recovery period after allo-HCT can take months to years. However, even years after allo-HCT patients have an increased risk to develop co-morbid conditions, e.g. metabolic or cardiovascular diseases [22]. On one hand, emerging research evidence indicates that these life style diseases are associated with physical inactivity. On the other hand, studies show that hematological cancer survivors are less likely to be physically active. Moreover, changing exercise behavior requires longer, individually adapted interventions. To enhance motivation and adherence, the PETRA study uses goal setting methods, and individual barriers are discussed during regular phone calls. These components have been shown to improve adherence [71]. Furthermore, PETRA helps patients to integrate in an exercise facility close to their home or give them the possibility to perform an internet-based training program. All these efforts may help patients to change the physical activity behavior in the long term. Finally, if during or at the end of the exercise intervention beneficial effects are detected, it is of interest whether those benefits sustain over a longer period of time.

Strengths of the PETRA study are the rigorous study design with a large sample size, adequately powered for the primary endpoint survival, and a broad range of assessments, including gold-standard methods for physical fitness and physical activity. Therefore,

PETRA provides a unique opportunity to examine the interaction of exercise/ physical activity on the haematological system and GvHD reaction. A further strength is the choice of the control group (relaxation training). Previous exercise RCT used typically usual care as comparison groups. Thus, it is unclear to what extent the observed effects are based on the physical exercise effect itself, or rather on psycho-social factors related to social support or attention by the trainer. This factor is particularly important when psychosocial outcomes are measured.

Summary

Previous studies in allo-HCT patients established first evidence about beneficial effects of exercise interventions on physical and psychosocial outcomes. However, the focus changed to more clinically relevant endpoints, e.g. prognosis. To our knowledge, no study has yet investigated a possible effect of exercise on overall survival after allo-HCT. Furthermore, there is a need for a better understanding of the physiological and psychological effects of exercise and their biological mechanisms in patients during and after allo-HCT. The PETRA study will provide a comprehensive picture of the potential effects of exercise during and after allo-HCT on overall survival, reducing side-effects and complications, and improving quality of life. We anticipate that our study will help to refine exercise guidelines for allo-HCTpatients.

List of abbreviations

ACSM: American College of Sports Medicine; AEs: Adverse events; BIA: Bioelectrical impedance analysis; CRP: C-reactive protein;
CPET: Cardiopulmonary exercise test;
GvHD: Graft-versus-host disease; IL-6: Interleukin-6; KPS: Karnofsky Peformance Scale;
MFI: Multidimensional Fatigue Inventory;
NCCN: National Comprehensive Cancer Network; NRM: Non-relapse mortality; QoL: Quality of life; RCTs: Randomized controlled trials; SAEs: Serious adverse events; TM: total mortality; TNF-α: Tumor necrosis factor alpha; $VO2_{peak}$: Maximum oxygen uptake

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

JW, GH, MB conception, design, trial protocol; JW, RK, CMU initiation and implementation of the study; JW and RK conception and supervision of exercise intervention and physical performance diagnostics; RK study coordinator, endpoint assessments; PD study physician; JW, RK and NK data management and statistical analysis; JW and RK drafted and finalized the manuscript. GH, MB, PD, CMU reviewed the manuscript. All authors have read and approved the final manuscript.

Acknowledgements and funding

The PETRA study is funded by the Deutsche José Carreras Leukämie Stiftung (project no. R10/42pf and R13/27) and supported by the NCT Liquid Biobank.

References

1. Copelan, E.A.: **Hematopoietic stem-cell transplantation.** N Engl J Med 2006. **354**(17): p. 1813-26.
2. Cramp, F. and J. Byron-Daniel: **Exercise for the management of cancer-related fatigue in adults.** Cochrane Database Syst Rev 2012. **11**: p. CD006145.
3. Knols, R., N.K. Aaronson, D. Uebelhart, J. Fransen, and G. Aufdemkampe: **Physical exercise in cancer patients during and after medical treatment: a systematic review of randomized and controlled clinical trials.** J Clin Oncol 2005. **23**(16): p. 3830-42.
4. Spence, R.R., K.C. Heesch, and W.J. Brown: **Exercise and cancer rehabilitation: a systematic review.** Cancer Treat Rev 2010. **36**(2): p. 185-94.
5. Speck, R.M., K.S. Courneya, L.C. Masse, S. Duval, and K.H. Schmitz: **An update of controlled physical activity trials in cancer survivors: a systematic review and meta-analysis.** J Cancer Surviv 2010. **4**(2): p. 87-100.
6. Schmitz, K.H., K.S. Courneya, C. Matthews, W. Demark-Wahnefried, D.A. Galvao, B.M. Pinto, M.L. Irwin, K.Y. Wolin, R.J. Segal, A. Lucia, C.M. Schneider, V.E. von Gruenigen, and A.L. Schwartz: **American College of Sports Medicine roundtable on exercise guidelines for cancer survivors.** Med Sci Sports Exerc 2010. **42**(7): p. 1409-26.
7. Wiskemann, J. and G. Huber: **Physical exercise as adjuvant therapy for patients undergoing hematopoietic stem cell transplantation.** Bone Marrow Transplant 2008. **41**(4): p. 321-9.
8. Coleman, E.A., S.K. Coon, R.L. Kennedy, K.D. Lockhart, C.B. Stewart, E.J. Anaissie, and B. Barlogie: **Effects of exercise in combination with epoetin alfa during high-dose chemotherapy and autologous peripheral blood stem cell transplantation for multiple myeloma.** Oncol Nurs Forum 2008. **35**(3): p. E53-61.
9. Shelton, M.L., J.Q. Lee, G.S. Morris, P.R. Massey, D.G. Kendall, M.F. Munsell, K.O. Anderson, M.J. Simmonds, and S.A. Giralt: **A randomized control trial of a supervised versus a self-directed exercise program for allogeneic stem cell transplant patients.** Psychooncology 2008. **18**(4): p. 353-9.
10. Jarden, M., M.T. Baadsgaard, D.J. Hovgaard, E. Boesen, and L. Adamsen: **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): p. 725-37.
11. Hacker, E.D., J. Larson, A. Kujath, D. Peace, D. Rondelli, and L. Gaston: **Strength training following hematopoietic stem cell transplantation.** Cancer Nurs 2011. **34**(3): p. 238-49.
12. Knols, R.H., E.D. de Bruin, K. Shirato, D. Uebelhart, and N.K. Aaronson: **Physical activity interventions to improve daily walking activity in cancer survivors.** BMC Cancer 2010. **10**: p. 406.
13. Wiskemann, J., P. Dreger, R. Schwerdtfeger, A. Bondong, G. Huber, N. Kleindienst, C.M. Ulrich, and M. Bohus: **Effects of a partly self-administered**

exercise program before, during, and after allogeneic stem cell transplantation. Blood 2011. **117**(9): p. 2604-13.
14. Persoon, S., M.J. Kersten, K. van der Weiden, L.M. Buffart, F. Nollet, J. Brug, and M.J. Chinapaw: **Effects of exercise in patients treated with stem cell transplantation for a hematologic malignancy: a systematic review and meta-analysis.** Cancer Treat Rev 2013. **39**(6): p. 682-90.
15. Morishita, S., K. Kaida, K. Ikegame, S. Yoshihara, K. Taniguchi, M. Okada, N. Kodama, H. Ogawa, and K. Domen: **Impaired physiological function and health-related QOL in patients before hematopoietic stem-cell transplantation.** Support Care Cancer 2012. **20**(4): p. 821-9.
16. White, A.C., N. Terrin, K.B. Miller, and H.F. Ryan: **Impaired respiratory and skeletal muscle strength in patients prior to hematopoietic stem-cell transplantation.** Chest 2005. **128**(1): p. 145-52.
17. Lakoski, S.G., N.D. Eves, P.S. Douglas, and L.W. Jones: **Exercise rehabilitation in patients with cancer.** Nat Rev Clin Oncol 2012. **9**(5): p. 288-96.
18. Bellizzi, K.M., J.H. Rowland, N.K. Arora, A.S. Hamilton, M.F. Miller, and N.M. Aziz: **Physical activity and quality of life in adult survivors of non-Hodgkin's lymphoma.** J Clin Oncol 2009. **27**(6): p. 960-6.
19. Andrykowski, M.A., M.M. Bishop, E.A. Hahn, D.F. Cella, J.L. Beaumont, M.J. Brady, M.M. Horowitz, K.A. Sobocinski, J.D. Rizzo, and J.R. Wingard: **Long-term health-related quality of life, growth, and spiritual well-being after hematopoietic stem-cell transplantation.** J Clin Oncol 2005. **23**(3): p. 599-608.
20. Ferrara, J.L., J.E. Levine, P. Reddy, and E. Holler: **Graft-versus-host disease.** Lancet 2009. **373**(9674): p. 1550-61.
21. Mitchell, S.A., N.K. Leidy, K.H. Mooney, W.N. Dudley, S.L. Beck, P.C. LaStayo, E.W. Cowen, P. Palit, L.E. Comis, M.C. Krumlauf, D.N. Avila, N. Atlam, D.H. Fowler, and S.Z. Pavletic: **Determinants of functional performance in long-term survivors of allogeneic hematopoietic stem cell transplantation with chronic graft-versus-host disease (cGVHD).** Bone Marrow Transplant 2010. **45**(4): p. 762-9.
22. Mosher, C.E., W.H. Redd, C.M. Rini, J.E. Burkhalter, and K.N. DuHamel: **Physical, psychological, and social sequelae following hematopoietic stem cell transplantation: a review of the literature.** Psychooncology 2009. **18**(2): p. 113-27.
23. Tichelli, A., A. Rovo, and A. Gratwohl: **Late pulmonary, cardiovascular, and renal complications after hematopoietic stem cell transplantation and recommended screening practices.** Hematology Am Soc Hematol Educ Program 2008: p. 125-33.
24. Baker, K.S., S. Armenian, and S. Bhatia: **Long-term consequences of hematopoietic stem cell transplantation: current state of the science.** Biol Blood Marrow Transplant 2010. **16**(1 Suppl): p. S90-6.
25. NCCN Clinical Practice Guidelines in Oncology. *Cancer-Related Fatigue*. 2014 [cited 2013 03.01.]; Available from: http://www.nccn.org/professionals/physician_gls/PDF/fatigue.pdf.
26. Bevans, M.F., S.A. Mitchell, and S. Marden: **The symptom experience in the first 100 days following allogeneic hematopoietic stem cell transplantation (HSCT).** Support Care Cancer 2008. **16**(11): p. 1243-54.
27. Al-Majid, S. and D.P. Gray: **A biobehavioral model for the study of exercise interventions in cancer-related fatigue.** Biol Res Nurs 2009. **10**(4): p. 381-91.
28. Ryan, J.L., J.K. Carroll, E.P. Ryan, K.M. Mustian, K. Fiscella, and G.R. Morrow: **Mechanisms of cancer-related fatigue.** Oncologist 2007. **12 Suppl 1**: p. 22-34.
29. Bergenthal, N., A. Will, F. Streckmann, K.D. Wolkewitz, I. Monsef, A. Engert, T. Elter, and N. Skoetz: **Aerobic physical exercise for adult patients with haematological malignancies.** Cochrane Database Syst Rev 2014. **11**: p. CD009075.
30. Ballard-Barbash, R., C.M. Friedenreich, K.S. Courneya, S.M. Siddiqi, A. McTiernan, and C.M. Alfano: **Physical activity, biomarkers, and disease outcomes in cancer survivors: a systematic review.** J Natl Cancer Inst 2012. **104**(11): p. 815-40.
31. Jones, L.W., D. Watson, J.E. Herndon, 2nd, N.D. Eves, B.E. Haithcock, G. Loewen, and L. Kohman: **Peak oxygen consumption and long-term all-cause mortality in nonsmall cell lung cancer.** Cancer 2010. **116**(20): p. 4825-32.
32. Courneya, K.S., R.J. Segal, D.C. McKenzie, H. Dong, K. Gelmon, C.M. Friedenreich, Y. Yasui, R.D. Reid, J.J. Crawford, and J.R. Mackey: **Effects of exercise during adjuvant chemotherapy on breast cancer outcomes.** Med Sci Sports Exerc 2014. **46**(9): p. 1744-51.
33. Wood, W.A., A.M. Deal, B.B. Reeve, A.P. Abernethy, E. Basch, S.A. Mitchell, C. Shatten, Y. Hie Kim, J. Whitley, J.S. Serody, T. Shea, and C. Battaglini: **Cardiopulmonary fitness in patients undergoing hematopoietic SCT: a pilot study.** Bone Marrow Transplant 2013. **48**(10): p. 1342-9.
34. Guilfoyle, R., A. Demers, C. Bredeson, E. Richardson, M. Rubinger, D. Szwajcer, and M.D. Seftel: **Performance status, but not the hematopoietic cell transplantation comorbidity index (HCT-CI), predicts mortality at a Canadian transplant center.** Bone Marrow Transplant 2009. **43**(2): p. 133-9.
35. Wiskemann, J., N. Kleindienst, R. Kuehl, P. Dreger, R. Schwerdtfeger, and M. Bohus: **Effects of physical exercise on survival after allogeneic stem cell transplantation.** Int J Cancer 2015.
36. Drouin, J.M., T.C. Valovich-mcLeod, S.J. Shultz, B.M. Gansneder, and D.H. Perrin: **Reliability and validity of the Biodex system 3 pro isokinetic dynamometer velocity, torque and position measurements.** Eur J Appl Physiol 2004. **91**(1): p. 22-9.
37. Eitzen, I., K.A. Hakestad, and M.A. Risberg: **Inter- and intrarater reliability of isokinetic thigh muscle strength tests in postmenopausal women with osteopenia.** Arch Phys Med Rehabil 2012. **93**(3): p. 420-7.
38. Webber, S.C. and M.M. Porter: **Reliability of ankle isometric, isotonic, and isokinetic strength and power testing in older women.** Phys Ther 2010. **90**(8): p. 1165-75.
39. Bohannon, R.W.: **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): p. 26-32.
40. Knols, R.H., E.D. de Bruin, D. Uebelhart, G. Aufdemkampe, U. Schanz, F. Stenner-Liewen, F. Hitz, C. Taverna, and N.K. Aaronson: **Effects of an outpatient physical exercise program on hematopoietic stem-cell transplantation recipients: a randomized clinical trial.** Bone Marrow Transplant 2011. **46**(9): p. 1245-55.
41. Mello, M., C. Tanaka, and F.L. Dulley: **Effects of an exercise program on muscle performance in patients undergoing allogeneic bone marrow transplantation.** Bone Marrow Transplant 2003. **32**(7): p. 723-8.

42. Jones, L.W., N.D. Eves, M. Haykowsky, A.A. Joy, and P.S. Douglas: **Cardiorespiratory exercise testing in clinical oncology research: systematic review and practice recommendations.** Lancet Oncol 2008. **9**(8): p. 757-65.
43. Steins Bisschop, C.N., M.J. Velthuis, H. Wittink, K. Kuiper, T. Takken, W.J. van der Meulen, E. Lindeman, P.H. Peeters, and A.M. May: **Cardiopulmonary exercise testing in cancer rehabilitation: a systematic review.** Sports Med 2012. **42**(5): p. 367-79.
44. Kelsey, C.R., J.M. Scott, A. Lane, E. Schwitzer, M.J. West, S. Thomas, J.E. Herndon, 2nd, M.G. Michalski, M.E. Horwitz, T. Hennig, and L.W. Jones: **Cardiopulmonary exercise testing prior to myeloablative allo-SCT: a feasibility study.** Bone Marrow Transplant 2014. **49**(10): p. 1330-6.
45. Crapo, R., R. Casaburi, A. Coaties, P. Enright, N. MacIntyre, P. McKay, D.H. Johnson, J. Wanger, and R. Zeballos: **ATS statement: guidelines for the six-minute walk test.** Am J Respir Crit Care Med 2002. **166**(1): p. 111-7.
46. Enright, P.L. and D.L. Sherrill: **Reference equations for the six-minute walk in healthy adults.** Am J Respir Crit Care Med 1998. **158**(5 Pt 1): p. 1384-7.
47. Valentinuzzi, M.E.: **Bioelectrical impedance techniques in medicine. Part I: Bioimpedance measurement. First section: general concepts.** Crit Rev Biomed Eng 1996. **24**(4-6): p. 223-55.
48. Segal, K.R., S. Burastero, A. Chun, P. Coronel, R.N. Pierson, Jr., and J. Wang: **Estimation of extracellular and total body water by multiple-frequency bioelectrical-impedance measurement.** Am J Clin Nutr 1991. **54**(1): p. 26-9.
49. Butte, N.F., U. Ekelund, and K.R. Westerterp: **Assessing physical activity using wearable monitors: measures of physical activity.** Med Sci Sports Exerc 2012. **44**(1 Suppl 1): p. S5-S12.
50. Hacker, E., C. Ferrans, E. Verlen, F. Ravandi, K. Besien, J. Gelms, and N. Dieterle: **Farigue and Physival Aktivity in Patients Undergoing Hematopoietic Stem Cell Transplant.** Oncol Nurs Forum 2006. **33**(3): p. 614-624.
51. Aaronson, N.K., S. Ahmedzai, B. Bergman, M. Bullinger, and A. Cull: **The European Organization for Research and Treatment of Cancer QLQ-C30: A Quality-of-Life Instrument for Use in International Clinical Trials in Oncology.** Journal of the National Cancer Institute 1993. **8**: p. 365-376.
52. Velikova, G., J. Weis, M.J. Hjermstad, M. Kopp, P. Morris, M. Watson, and O. Sezer: **The EORTC QLQ-HDC29: a supplementary module assessing the quality of life during and after high-dose chemotherapy and stem cell transplantation.** Eur J Cancer 2007. **43**(1): p. 87-94.
53. Grulke, N., C. Albani, and H. Bailer: **Quality of life in patients before and after haematopoietic stem cell transplantation measured with the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Core Questionnaire QLQ-C30.** Bone Marrow Transplant 2012. **47**(4): p. 473-82.
54. Schwarz, R. and A. Hinz: **Reference data for the quality of life questionnaire EORTC QLQ-C30 in the general German population.** Eur J Cancer 2001. **37**(11): p. 1345-51.
55. Cocks, K., M.T. King, G. Velikova, M. Martyn St-James, P.M. Fayers, and J.M. Brown: **Evidence-based guidelines for determination of sample size and interpretation of the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30.** J Clin Oncol 2011. **29**(1): p. 89-96.
56. Smets, E.M., B. Garssen, B. Bonke, and J.C. De Haes: **The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue.** J Psychosom Res 1995. **39**(3): p. 315-25.
57. Schwarz, R., O. Krauss, and A. Hinz: **Fatigue in the general population.** Onkologie 2003. **26**(2): p. 140-4.
58. Bower, J.E., K. Bak, A. Berger, W. Breitbart, C.P. Escalante, P.A. Ganz, H.H. Schnipper, C. Lacchetti, J.A. Ligibel, G.H. Lyman, M.S. Ogaily, W.F. Pirl, P.B. Jacobsen, and O. American Society of Clinical: **Screening, assessment, and management of fatigue in adult survivors of cancer: an American Society of Clinical oncology clinical practice guideline adaptation.** J Clin Oncol 2014. **32**(17): p. 1840-50.
59. National Comprehensive Cancer, N.: **Distress management. Clinical practice guidelines.** J Natl Compr Canc Netw 2003. **1**(3): p. 344-74.
60. Mehnert, A., D. Mueller, C. Lehmann, and U. Koch: **The German Version of the NCCN Distress Thermometer: Validation of a Screening Instrument for Assessment of Psychosocial Distress in Cancer Patients.** Zeitschrift für Psychiatrie und Psychotherapie 2006. **54**(3): p. 213-223.
61. Ransom, S., P.B. Jacobsen, and M. Booth-Jones: **Validation of the Distress Thermometer with bone marrow transplant patients.** Psychooncology 2006. **15**(7): p. 604-12.
62. Schroevers, M.J., R. Sanderman, E. van Sonderen, and A.V. Ranchor: **The evaluation of the Center for Epidemiologic Studies Depression (CES-D) scale: Depressed and Positive Affect in cancer patients and healthy reference subjects.** Qual Life Res 2000. **9**(9): p. 1015-29.
63. Lohaus, A. and G. Schmitt, *Fragebogen zur Erhebung von Kontrollüberzeugung zu Krankheit und Gesundheit (KKG). Handanweisung*. 1989, Göttingen, Toronto, Zürich: Hogrefe.
64. Wallston, K.A., B.S. Wallston, and R. DeVellis: **Development of the Multidimensional Health Locus of Control (MHLC) Scales.** Health Educ Monogr 1978. **6**(2): p. 160-70.
65. Reitan, R.M.: **The relation of the trail making test to organic brain damage.** J Consult Psychol 1955. **19**(5): p. 393-4.
66. Sanchez-Cubillo, I., J.A. Perianez, D. Adrover-Roig, J.M. Rodriguez-Sanchez, M. Rios-Lago, J. Tirapu, and F. Barcelo: **Construct validity of the Trail Making Test: role of task-switching, working memory, inhibition/interference control, and visuomotor abilities.** J Int Neuropsychol Soc 2009. **15**(3): p. 438-50.
67. Thomas, E.D., R. Storb, R.A. Clift, A. Fefer, L. Johnson, P.E. Neiman, K.G. Lerner, H. Glucksberg, and C.D. Buckner: **Bone-marrow transplantation (second of two parts).** N Engl J Med 1975. **292**(17): p. 895-902.
68. Beller, E.M., V. Gebski, and A.C. Keech: **Randomisation in clinical trials.** Med J Aust 2002. **177**(10): p. 565-7.
69. Garber, C.E., B. Blissmer, M.R. Deschenes, B.A. Franklin, M.J. Lamonte, I.M. Lee, D.C. Nieman, D.P. Swain, and M. American College of Sports: **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): p. 1334-59.
70. American College of Sports, M.: **American College of Sports Medicine position stand. Progression models**

in resistance training for healthy adults. Med Sci Sports Exerc 2009. **41**(3): p. 687-708.

71. Bourke, L., K.E. Homer, M.A. Thaha, L. Steed, D.J. Rosario, K.A. Robb, J.M. Saxton, and S.J. Taylor: **Interventions for promoting habitual exercise in people living with and beyond cancer.** Cochrane Database Syst Rev 2013. **9**: p. CD010192.
72. Winters-Stone, K.M., S.E. Neil, and K.L. Campbell: **Attention to principles of exercise training: a review of exercise studies for survivors of cancers other than breast.** Br J Sports Med 2014. **48**(12): p. 987-995.
73. Bernstein, D. and T. Borkovec: **Progressive relaxation training: A manual for the helping profession.** Champaign, IL: Research Press 1973.
74. Yang, L. and A. Tsiatis: **Efficiency Study of Estimators for a Treatment Effect in a Pretest-Posttest Trial.** Am Stat 2001. **55**: p. 314-21.
75. Beavers, K.M., T.E. Brinkley, and B.J. Nicklas: **Effect of exercise training on chronic inflammation.** Clin Chim Acta 2010. **411**(11-12): p. 785-93.
76. Fairey, A.S., K.S. Courneya, C.J. Field, G.J. Bell, L.W. Jones, B.S. Martin, and J.R. Mackey: **Effect of exercise training on C-reactive protein in postmenopausal breast cancer survivors: a randomized controlled trial.** Brain Behav Immun 2005. **19**(5): p. 381-8.
77. Donges, C.E., R. Duffield, and E.J. Drinkwater: **Effects of resistance or aerobic exercise training on interleukin-6, C-reactive protein, and body composition.** Med Sci Sports Exerc 2010. **42**(2): p. 304-13.
78. Campbell, P.T., K.L. Campbell, M.H. Wener, B.L. Wood, J.D. Potter, A. McTiernan, and C.M. Ulrich: **A yearlong exercise intervention decreases CRP among obese postmenopausal women.** Med Sci Sports Exerc 2009. **41**(8): p. 1533-9.
79. Petersen, A.M. and B.K. Pedersen: **The anti-inflammatory effect of exercise.** J Appl Physiol 2005. **98**(4): p. 1154-62.
80. Pierce, B.L., R. Ballard-Barbash, L. Bernstein, R.N. Baumgartner, M.L. Neuhouser, M.H. Wener, K.B. Baumgartner, F.D. Gilliland, B.E. Sorensen, A. McTiernan, and C.M. Ulrich: **Elevated biomarkers of inflammation are associated with reduced survival among breast cancer patients.** J Clin Oncol 2009. **27**(21): p. 3437-44.
81. Fiuza-Luces, C., L. Soares-Miranda, A. Gonzalez-Murillo, J.M. Palacio, I. Colmenero, F. Casco, G.J. Melen, A. Delmiro, M. Moran, M. Ramirez, and A. Lucia: **Exercise Benefits in Chronic Graft versus Host Disease: A Murine Model Study.** Med Sci Sports Exerc 2013. **45**(9): p. 1703-1711.
82. Dietrich, S., C.S. Falk, A. Benner, S. Karamustafa, E. Hahn, M. Andrulis, U. Hegenbart, A.D. Ho, P. Dreger, and T. Luft: **Endothelial vulnerability and endothelial damage are associated with risk of graft-versus-host disease and response to steroid treatment.** Biol Blood Marrow Transplant 2013. **19**(1): p. 22-7.
83. Luft, T., S. Dietrich, C. Falk, M. Conzelmann, M. Hess, A. Benner, F. Neumann, B. Isermann, U. Hegenbart, A.D. Ho, and P. Dreger: **Steroid-refractory GVHD: T-cell attack within a vulnerable endothelial system.** Blood 2011. **118**(6): p. 1685-92.
84. Lin, M.T., B. Storer, P.J. Martin, L.H. Tseng, T. Gooley, P.J. Chen, and J.A. Hansen: **Relation of an interleukin-10 promoter polymorphism to graft-versus-host disease and survival after hematopoietic-cell transplantation.** N Engl J Med 2003. **349**(23): p. 2201-10.
85. Choi, S.W., C.L. Kitko, T. Braun, S. Paczesny, G. Yanik, S. Mineishi, O. Krijanovski, D. Jones, J. Whitfield, K. Cooke, R.J. Hutchinson, J.L. Ferrara, and J.E. Levine: **Change in plasma tumor necrosis factor receptor 1 levels in the first week after myeloablative allogeneic transplantation correlates with severity and incidence of GVHD and survival.** Blood 2008. **112**(4): p. 1539-42.
86. Zeng, D., D. Lewis, S. Dejbakhsh-Jones, F. Lan, M. Garcia-Ojeda, R. Sibley, and S. Strober: **Bone marrow NK1.1(-) and NK1.1(+) T cells reciprocally regulate acute graft versus host disease.** J Exp Med 1999. **189**(7): p. 1073-81.
87. Palmer, J.M., K. Rajasekaran, M.S. Thakar, and S. Malarkannan: **Clinical relevance of natural killer cells following hematopoietic stem cell transplantation.** J Cancer 2013. **4**(1): p. 25-35.
88. Na, Y.M., M.Y. Kim, Y.K. Kim, Y.R. Ha, and D.S. Yoon: **Exercise therapy effect on natural killer cell cytotoxic activity in stomach cancer patients after curative surgery.** Arch Phys Med Rehabil 2000. **81**(6): p. 777-9.
89. Timmons, B.W. and T. Cieslak: **Human natural killer cell subsets and acute exercise: a brief review.** Exerc Immunol Rev 2008. **14**: p. 8-23.
90. Kim, S. and H. Kim: **A series of bed exercises to improve lymphocyte count in allogenic bone marrow transplantation patients.** European Journal of Cancer Care 2006. **15**: p. 453-457.
91. Kim, D.H., J.G. Kim, S.K. Sohn, W.J. Sung, J.S. Suh, K.S. Lee, and K.B. Lee: **Clinical impact of early absolute lymphocyte count after allogeneic stem cell transplantation.** Br J Haematol 2004. **125**(2): p. 217-24.
92. Shilling, H.G., K.L. McQueen, N.W. Cheng, J.A. Shizuru, R.S. Negrin, and P. Parham: **Reconstitution of NK cell receptor repertoire following HLA-matched hematopoietic cell transplantation.** Blood 2003. **101**(9): p. 3730-40.
93. Dimeo, F., S. Fetscher, W. Lange, R. Mertelsmann, and J. Keul: **Effects of aerobic exercise on the physical performance and incidence of treatment-related complications after high-dose chemotherapy.** Blood 1997. **90**(9): p. 3390-4.
94. Bower, J.E.: **Cancer-related fatigue--mechanisms, risk factors, and treatments.** Nat Rev Clin Oncol 2014. **11**(10): p. 597-609.
95. Wang, X.S., Q. Shi, L.A. Williams, C.S. Cleeland, G.M. Mobley, J.M. Reuben, B.N. Lee, and S.A. Giralt: **Serum interleukin-6 predicts the development of multiple symptoms at nadir of allogeneic hematopoietic stem cell transplantation.** Cancer 2008. **113**(8): p. 2102-9.
96. Meyers, C.A., M. Albitar, and E. Estey: **Cognitive impairment, fatigue, and cytokine levels in patients with acute myelogenous leukemia or myelodysplastic syndrome.** Cancer 2005. **104**(4): p. 788-93.
97. Jarden, M., K. Nelausen, D. Hovgaard, E. Boesen, and L. Adamsen: **The effect of a multimodal intervention on treatment-related symptoms in patients undergoing hematopoietic stem cell transplantation: a randomized controlled trial.** J Pain Symptom Manage 2009. **38**(2): p. 174-90.

4 Manuscript III

Published in Medicine & Science in Sports & Exercise (MSSE)
Issue: 47
Pages: 889-959
Impact Factor: 4.48 (2013)
Submitted: 12 June 2014
Revised: 22 August 2014
Accepted for publication: 29 August 2014 (published ahead of print)

Exercise intensity classification in cancer patients undergoing allogeneic HCT

Rea Kuehl[1], Friederike Scharhag-Rosenberger[1,2], Kai Schommer[3], Martina E. Schmidt[1], Peter Dreger[4], Gerhard Huber[5], Martin Bohus[6], Cornelia M. Ulrich[1,7], and Joachim Wiskemann[1,2]

[1] Division of Preventive Oncology, National Center for Tumor Diseases (NCT) and German Cancer Research Center, Heidelberg, Germany
[2] Department of Medical Oncology, National Center for Tumor Diseases (NCT) and Heidelberg University Hospital, Heidelberg, Germany
[3]Department of Medicine VII, Heidelberg University Hospital, Heidelberg, Germany
[4]Department of Medicine V, Heidelberg University Hospital, Heidelberg, Germany
[5]Institute of Sports and Sport Science, Heidelberg University, Heidelberg, Germany
[6]Central Institute of Mental Health, Mannheim, Germany
[7]Fred Hutchinson Cancer Research Centre, Seattle, United States

ABSTRACT

Objective: Exercise intervention studies during and after cancer treatment show beneficial effects for various physical and psychosocial outcomes. Current exercise intensity guidelines for cancer patients are rather general and have been adapted from ACSM recommendations for healthy individuals. Intensive cancer treatment regimens such as allogeneic stem cell transplantation (allo-HCT) may change the cardiovascular response to acute exercise. Therefore, we evaluated the relationships between %VO2 reserve (%VO2R, reference) and %HRR, %HRmax, and %VO2max and compared calculated intensities to given intensities by ACSM. **Methods:** Measurements prior to and 180 days after allo-HCT from a randomized, controlled trial were used. Only patients who reached maximal effort and at least two exercise stages in our maximal incremental cycling test were included. Prior to allo-HCT, 106 patients were included, and 180 days after treatment, 49 patients met our inclusion criteria. Individual regression lines were calculated with VO2R as the reference. Calculated exercise intensities for endurance training prescription were compared to ACSM values. **Results:** Prior to allo-HCT, %HRR values of patients were significantly lower than ACSM values, and %HRmax and %VO2max values were significantly higher (except 90% HRmax, which was significantly lower, all $p<.01$). 180 days after allo-HCT, values for %HRR were not significantly different to ACSM values (except 90%, which was significantly lower, $p=.01$), whereas %HRmax and %VO2max were significantly higher (all $p<.05$). Furthermore, regression models revealed no influence of beta-blockers on calculated intensities. **Conclusions:** ACSM's exercise intensity recommendations for endurance training may not be applicable for cancer patients during and 180 days after allo-HCT because they may not meet the targeted intensity class, with the exception of %HRR 180 days after allo-HCT.
Keywords: exercise, cancer, intensity, transplantation, oncology

INTRODUCTION

Exercise intervention studies in hematological cancer patients during and after therapy have demonstrated safety and beneficial effects on physiological and psychological outcomes (26, 36, 37). The accumulating evidence about beneficial effects of exercise in cancer survivors has led the American College of Sports Medicine (ACSM) to develop exercise guidelines for cancer survivors; it is recommended to perform aerobic exercise for 150 minutes per week with moderate, or 75 minutes per week with vigorous intensity (27). These guidelines were adapted from existing recommendations for exercise from the ACSM for healthy individuals (13) noting that exercise programs in cancer survivors may need to be modified considering health status and treatment received. (27) Thus, the guidelines do not provide exact training intensities as a result of a lack of information in previous studies (4). However, prescription of adequate intensity is crucial for both adequate training stimulus and control for exercise related risks; further, appropriate prescriptions are essential in terms of exploring dose-response effects (35). ACSM guidelines for healthy individuals recommend intensities for moderate endurance training of 40-59% heart rate reserve (HRR), 64-76% maximal heart rate (HR_{max}) or 46-63% maximal oxygen consumption (VO_{2max}) (13). Most exercise studies in hematological cancer patients that used exercise intensity prescriptions relied on commonly used equations for age-predicted HR_{max} estimates (e.g. *220-age* in years) (17, 19, 34).

However, the relationship between HR and VO_2 during exercise may be different in hematological cancer patients and might change over time. Allogeneic stem cell transplantation (allo-HCT) used in hematological cancers is a very intense treatment regimen which is comprised of high-dose chemotherapy, intake of immunosuppressants and high-dose corticosteroids, and in some cases, total body irradiation (7). A substantial amount of evidence has shown that cancer patients have a marked reduction in cardiorespiratory fitness as a result of the toxic effects of anti-cancer therapy and physical inactivity during and after treatment (18, 20). The causes are often multifactorial and involve pulmonary limitations after chest radiation, cardiac limitations after antracycline-containing chemotherapy or mediastinal radiation, low hemoglobin levels, or alterations in the skeletal muscle oxidative capacity (12, 20). Furthermore, even before transplantation, patients' physical performance is reduced (33) and a long period of drug intake after allo-HCT (e.g. immuno-suppressants and corticosteroids) is known to cause muscle wasting (21), which also may influence the addressed relationship.

Therefore, our aim was to investigate whether the ACSM intensity classification for healthy people and the application of age-predicted HR_{max} estimates are appropriate for endurance training prescriptions in hematological cancer patients prior to and after allo-HCT, and to examine if the relationship between VO_2 and HR changes after therapy. Thereby, age, gender, BMI, hemoglobin level and beta-blocker intake were considered as covariates.

METHODS

Design

Data were obtained from the PETRA study. The PETRA study is a randomized controlled ongoing one-year exercise intervention study in allo-HCT patients. Patients assigned to the experimental group (EG) received an endurance and resistance training program, whereas patients in the control group (CG) received a relaxation program. Patients conducted maximal cardiopulmonary exercise tests (CPET) at three time points. In the present analysis we included all patients who performed at least one maximal CPET at two different assessment time points, prior to allo-HCT and/or 180 days after, and completed a minimum of 2 exercise stages of the maximal CPET. The assessment time points were selected because they include the period of intensive treatment and appear to be a common time point for starting exercise in the context of a rehabilitation program. The study has been approved by the Ethics Committees of the University of Mannheim (number 2009-349N-MA) and Heidelberg (number S-021/2011) and is registered at ClinicalTrials.gov (NCT01374399). Written informed consent was obtained from each participant prior to first assessment.

Subjects

A total of 110 hematological cancer patients were included in the analysis. Exclusion criteria were premature exercise cessation due to medical reasons, or lack of maximal effort (exhaustion criteria: RER >1.1 or HR >85 % of age-predicted maximum (16, 25)). The most frequent disease was acute myeloid leukemia (n=28), followed by chronic myeloid leukemia (n=22), lymphoma (n=18), multiple myeloma (n=12), acute lymphatic leukemia (n=7), chronic lymphatic leukemia (n=6), and others (n=13). 43% (n=46) patients were in complete remission prior allo-HCT. Subjects' detailed characteristics are presented in table 1. Due to the following reasons we could not collect data in 61 patients for the second measurement point (180 days after allo-HCT): assessment point was not yet reached (n=21), patients died (n=16), drop-outs (n=6), medical reasons (n=8), and others (n=10). For four patients included in the second measurement point, we had no data for the first time point. At the

second measurement point 27 patients (55%) were in the EG.

Data collection

All maximal CPETs were performed on an electronically braked cycle ergometer (Ergoselect 100, Ergoline, Bitz, Germany) and were monitored by a physician. The test protocol was a graded procedure of two-minute stages starting at 50 W and increasing by 25 W until voluntary exhaustion or medical reasons for premature exercise cessation. Cadence was kept constant between 60 and 70 rpm. A 12-lead ECG was recorded continuously and blood pressure was measured every two minutes. Gas exchange measurements were performed continuously using a breath-by-breath system (Ergostik, Geratherm Respiratory, Bad Kissingen, Germany). The metabolic device was calibrated before each test according to the instructions provided by the manufacturer. Gas exchange data and HR were stationary time averaged over 30 s. VO_{2max} and HR_{max} were considered the highest 30 s average value during or immediately post exercise. Maximal respiratory exchange ratio (RER_{max}) was considered the highest 30 s average value during exercise.

TABLE 1. Subject characteristics before and 180 d after allo-HCT

	Before allo-HCT (*n*=106)	180 d after allo-HCT (*n*=49)
Age (yr)	52 ± 11	54 ± 11
Male	73 (69%)	36 (73%)
Female	33 (31%)	13 (27%)
Height (m)	1.73 ± 0.08	1.75 ± 0.10
Weight (kg)	80.46 ± 16.44	77.50 ± 14.73
BMI ($kg \cdot m^{-2}$)	26.31± 4.54	24.93 ± 4.17
Beta-blocker	22 (21%)	12 (25%)
VO_{2rest} ($L \cdot min^{-1}$)	0.34 ± 0.12	0.31 ± 0.10
VO_{2max} ($L \cdot min^{-1}$)	1.76 ± 0.50	1.68 ± 0.48
VO_2R ($L \cdot min^{-1}$)	1.42 ± 0.47	1.34 ± 0.45
P_{max} (W)	133 ± 36	132 ± 46
HR_{rest} (min^{-1})	79 ± 13	76 ± 16
HR_{max} (min^{-1})	159 ± 21	151 ± 23
HRR (min^{-1})	79 ± 21	75 ± 23
RER_{max}	1.23 ± 0.11	1.24 ± 0.11
Hb ($g \cdot dL^{-1}$)	11.80 ± 1.67	12.12 ± 1.33

Values are presented as means ± SD or frequencies.

Data extraction and statistical analysis

HR and VO_2 were assessed at the end of each exercise stage and at maximum. Ventilatory threshold (VT) was determined according to the V-Slope method (2). To calculate HRR and VO_2R, resting data were obtained from the resting period prior to the start of the exercise test in a sitting position on the cycle ergometer (VO_2) and in laying position during resting ECG (HR). HRR and VO_2R were calculated by subtracting the resting value from the maximum value. Values of each exercise stage were expressed in $\%VO_{2max}$, $\%HR_{max}$, $\%VO_2R$, %HRR, % of maximal power output ($\%P_{max}$), and %VT (the latter two are not part of the ACSM recommendations, but are commonly used for training prescriptions (6, 8)). After testing for normality, five linear regression analyses were calculated for each subject and test. We used $\%VO_2R$ as the independent variable (reference to define exercise classes), and $\%VO_{2max}$, $\%HR_{max}$, %HRR, $\%P_{max}$, or %VT as dependent variables, respectively. We selected VO_2R as the reference because reserve values are superior to maximal values and VO_2R represents the individual performance capacity (13). . The resulting individual regression equations were used to calculate the $\%VO_{2max}$, $\%HR_{max}$, %HRR, $\%P_{max}$, and %VT values that correspond to 30, 40, 60, and 90 % VO_2R, corresponding to the lower limit of light, moderate, vigorous , and near maximal intensity by ACSM. Additionally, we estimated HR_{max} and HRR with the equation 220-age (in years), as previously used in exercise studies. One-sample t-tests were used to compare the resulting values to the ACSM's expected values. To compare differences between the two time points paired t-tests were used. Furthermore, multiple regression models were applied to determine influence of beta-blocker intake (BB), age, gender, BMI, and hemoglobin level (Hb) on measured and calculated values. The probability of making a Type I error was set at $P < 0.05$. Statistical analyses were performed using SAS 9.3.

RESULTS

Comparison to ACSM values

Table 2a displays the results prior to transplantation. All %HRR, $\%HR_{max}$, and $\%VO_{2max}$ means, corresponding to 30, 40, 60, and 90 %VO2R, were significantly different from the ACSM's recommended values. Whereas the %HRR values of the patients were significantly lower than ACSM recommendations, $\%HR_{max}$ and $\%VO_{2max}$ values were significantly higher (except $90\%HR_{max}$). Additionally, VT was located at 40% of VO_2R. Figure 1 shows the regression lines for our patients in comparison to the ACSM values.

Table 2b displays the results 180 days after transplantation. Here, similar results for $\%HR_{max}$ and $\%VO_{2max}$ were observed as for the measurement time point prior to transplantation. For %HRR, there was no significant difference between ACSM recommendations and patients' values (except 90%HRR, where patients' values were still significantly lower). Group assignment (exercise vs. relaxation control) had no effect on regression lines180 days after transplantation, and paired t-tests showed no significant changes in%HRR, $\%HR_{max}$, and $\%VO_{2max}$ values over time (all $P > 0.05$).

TABLE 2a. Calculated exercise intensities before allo-HCT (*n*=106) in comparison to ACSM values.

$\%VO_2R$ Reference	%HRR ACSM	%HRR Cancer	$\%HR_{max}$ ACSM	$\%HR_{max}$ Cancer	$\%VO_{2max}$ ACSM	$\%VO_{2max}$ Cancer	$\%P_{max}$ Cancer	%VT (n=104) Cancer
30	30	24.56±14.10 CI:21.83-27.26 *P*<0.01	57	63.14±8.06 CI:61.60-64.71 *P* <0.01	37	44.08±4.57 CI:43.20-44.98 *P* <0.01	29.54±7.77 CI:28.06-31.05	83.96±14.43 CI: 81.14-86.75
40	40	34.76±12.41 CI:32.35-37.15 *P*<0.01	64	68.13±7.07 CI:66.77-69.50 *P* <0.01	46	52.07±3.90 CI:51.33-52.82 *P* <0.01	39.57±6.85 CI:38.25-40.90	99.37±17.13 CI: 96.02-102.70
60	60	55.14±9.66 CI:53.30-57.01 *P*<0.01	77	78.12±5.31 CI:77.08-79.13 *P* =0.03	64	68.04±2.61 CI:67.54-68.56 *P* <0.01	59.64±5.64 CI:58.54-60.71	130.18±23.40 CI:125.62-134.73
90	90	85.74±8.34 CI:84.13-87.36 *P*<0.01	96	93.08±4.21 CI:92.27-93.88 *P* <0.01	91	92.00±0.64 CI:91.89-92.14 *P* <0.01	89.72±6.22 CI:88.51-90.92	176.40±33.66 CI: 169.84-182.95

TABLE 2b. Calculated exercise Intensities 180 d after allo-HCT (*n*=49) in comparison to ACSM values.

$\%VO_2R$ Reference	%HRR ACSM	%HRR Cancer	$\%HR_{max}$ ACSM	$\%HR_{max}$ Cancer	$\%VO_{2max}$ ACSM	$\%VO_{2max}$ Cancer	$\%P_{max}$ Cancer	%VT (n=48) Cancer
30	30	28.75±18.97 CI:23.30-34.20 *P* =0.65	57	65.05±11.50 CI:61.75-8.34 *P* <0.01	37	44.05±4.40 CI:42.80-45.33 *P* <0.01	29.60±9.54 CI:26.83-32.37	80.42±14.18 CI: 76.32-84.55
40	40	38.34±16.23 CI:33.69-43.02 *P* =0.48	64	69.77±9.95 CI:66.90-72.63 *P* <0.01	46	52.04±3.76 CI:50.97-53.14 *P* <0.01	39.63±8.50 CI:37.18-42.12	95.23±16.41 CI: 90.46-100.00
60	60	57.56±11.27 CI:54.32-60.80 *P* =0.14	77	79.20±7.04 CI:77.19-81.22 *P* =0.03	64	68.02±2.52 CI:67.30-68.76 *P* <0.01	59.73±6.90 CI:57.73-61.72	124.82±21.56 CI:118.56-131.06
90	90	86.36±8.00 CI:84.06-88.67 *P* <0.01	96	93.38± 4.34 CI:92.13-94.63 *P* <0.01	91	92.01±0.63 CI:91.83-92.20 *P* <0.01	89.86±6.54 CI:87.96-91.75	169.20±30.02 CI: 160.49-177.92

Table 3 shows exercise intensity classes for patients prior to and 180 days after allo-HCT derived from our sample.

Comparison to predicted values from standard equation

%HRR values calculated with the equation *220-age* were significantly lower than the observed values at both time points (all $P > 0.01$). $\%HR_{max}$ values were significantly higher than observed values at both time points (all $P > 0.01$, see table 4).

Effects of potential biasing factors

Regression analysis revealed that the relationship between VO_2R and HR_{max} was not affected by beta-blocker intake, age, gender, BMI or hemoglobin level at all intensities (all $P > 0.05$).The VO_2R-HRR relationship was significantly influenced by age (R^2 11.7-12.6%, model: $P > 0.026$; age: all $P > 0.001$) in all models (except for $90\%VO_2R$) and the VO_2R-VO_{2max} relationship was significantly influenced by hemoglobin level (R^2 10.4%, model: $P > 0.049$; Hb: all $P = .019$) in all models. Since no influence of beta-blocker intake on calculated regressions was observed, we included all patients in the analysis.

DISCUSSION

To our knowledge, this is the first study evaluating ACSM's exercise intensity classification in cancer patients. Prior to allo-HCT, the %HRR values of our patients related to light, moderate or vigorous exercise (specified by %VO2R) were significantly lower than ACSM recommendations, while $\%HR_{max}$ and $\%VO_{2max}$ values were significantly higher (except for 90% HR_{max}). Similar results were observed 180 days after allo-HCT for$\%HR_{max}$ and $\%VO_{2max}$. In contrast, for %HRR the patient values did not differ significantly from ACSM recommendations (except 90% HRR). Our results indicate that the ACSM guidelines concerning endurance exercise intensity are not applicable prior to allo-HCT, because they did not meet the targeted intensity class. 180 days after transplantation, only30, 40, and 60% HRR were comparable to ACSM recommendations. Furthermore, when calculating HR_{max} with the equation *220-age*, values for %HRR and $\%HR_{max}$ significantly differed from measured values prior to and 180 days after transplantation.

TABLE 3a. Exercise intensity classes in cancer patients before allo-HCT (*n*=106).

Intensity	%VO_2R (Reference)	%HRR	%HR_{max}	%VO_{2max}	%P_{max}	%VT
Light	30 - 39	25 - 34	63 - 67	44 - 51	30 - 38	84 - 98
Moderate	40 - 59	35 - 54	68 - 77	52 - 67	39 - 59	99 - 129
Vigorous	60 - 89	55 - 85	78 - 92	68 - 91	60 - 89	130 - 175
Near-maximal	≥90	≥ 86	≥93	≥92	≥90	≥176

TABLE 3b. Exercise intensity classes in cancer patients 180 d after allo-HCT (*n*=49).

Intensity	%VO_2R (Reference)	%HRR	%HR_{max}	%VO_{2max}	%P_{max}	%VT
Light	30 - 39	29 - 37	65 - 69	44 - 51	30 - 39	80 - 94
Moderate	40 - 59	38 - 57	70 - 78	52 - 67	40 - 59	95 - 124
Vigorous	60 – 89	58 - 85	79 - 92	68 - 91	60 - 89	125 - 168
Near-maximal	≥90	≥ 86	≥93	≥92	≥90	≥169

TABLE 4a. Exercise intensities calculated by equation *220-age* before allo-HCT (*n*=106).

%VO_2R Reference	%HRR (Equation)	%HR_{max} (Equation)
30	24.28±16.61*,**	58.91±12.34*
	CI:19.51-29.05	CI:55.35-62.45
40	32.46±16.05*,**	63.23±11.75*
	CI:27.86-37.09	CI:59.87-66.62
60	48.82±15.54*,**	71.92±11.26*,**
	CI:44.02-53.62	CI:68.67-75.16
90	73.36±21.24*,**	84.92±12.42*,**
	CI:67.27-79.48	CI:81.35-88.50

*sig. difference to measured patients' values (*P*<0.05) ** sig. difference to ACSM values (*P* <0.05)

TABLE 4b. Exercise intensities calculated by equation *220-age* 180 d after allo-HCT (*n*=49).

%VO2R Reference	%HRR (Equation)	%HRmax (Equation)
30	22.64±13.54*,**	59.57±9.10*,**
	CI:20.03-25.25	CI:57.80-61.31
40	31.87±13.25*,**	64.32±8.86*
	CI:29.33-34.44	CI:62.60-66.01
60	50.33±14.51*,**	73.82±8.96*,**
	CI:47.54-53.14	CI:72.09-75.53
90	78.04±19.68*,**	88.05±10.52*,**
	CI:74.23-81.83	CI:86.04-90.09

*sig. difference to measured patients' values (*P* <0.05)
** sig. difference to ACSM values (*P* <0.05)

In healthy people, a dose-response relationship between exercise intensity and favorable effects occurs. Therefore, exercise prescription should ensure a sufficient training stimulus, a reasonable control during exercise sessions, but also avoid over-exertion (10). Thus, in cancer patients it is recommended to tailor exercise intensity to individual cardiopulmonary fitness levels. However, light to moderate intensity is recommended without any further definition (4, 27, 30). The Australian Association for Exercise and Sport Science published in their guidelines for cancer patients values of 50-75% VO_{2max} or HRR and 60-80% HR_{max} for moderate intensity, but it remains unclear if the data were derived from a cancer population (15). In comparison to these guidelines, percentages of HRR in our patients were considerably below the recommended percentages (50-75% HRR vs. 35-54% HRR prior to and 38-57% HRR 180 days after) for moderate intensity. The application of these guidelines would have led to a prescription of higher exercise intensity than targeted. Therefore, we provide tables with exercise intensities for endurance training prescription that were derived from a sample of hematological cancer patients. These tables can be used to determine exercise intensity prior to and 180 days after allo-HCT and should be of major clinical interest.

Some studies investigated the relationship between HR and VO_2 proposed by ACSM in various populations. Swain and Leutholzer demonstrated that in low-fit subjects, the relationship was significantly different from the ACSM values (32), whereas Lounana et al. concluded that in highly-trained subjects the ACSM values were not applicable (22). Furthermore, in patients with heart disease, (3, 24) chronic obstructive pulmonary disease (COPD), (29) and obese individuals (5), the proposed percent values from the ACSM significantly differed from the calculated percent values in the different studies. Moreover, most of the studies as well as the ACSM, used pooled group data to establish the intensity categories, but it is more appropriate to perform a linear regression for each subject and then calculate the mean regression equation (31). In our analyses we used the aforementioned approach and calculated individual linear regression equations accordingly.

Furthermore, the precise reporting of exercise intensity is critical to allow exact comparisons between training studies. In hematological cancer patients during and after HCT, most studies that used CPET applied submaximal ergometer or treadmill tests (1, 17, 34), very few small studies applied maximal tests (6, 14). For training intensity prescription, percentages of HR_{max} and HRR were

widely used and the intensity varied between 40% and 90% HR_{max} (11, 14, 19, 28, 34). However, most studies used formulas for age-predicted HR_{max} estimates for defining exercise intensities. For example, one exercise program beginning 180 days after HCT, started at 50-60%HR_{max} and increased intensity up to 70-80 %HR_{max} (19). By categorizing these intensities based on our results, 50-60 %HR_{max} represents a very light intensity (light intensity started at 65%), whereas 70-80% HR_{max} falls in the vigorous intensity classification. Another study, examining endurance training during chemotherapy, used 70% HR_{max} as an intensity target. This intensity was carried out five times in an interval training pattern with 3-minutes interval (11). In comparison to our data, this would correspond to a moderate-to-vigorous intensity. Thus, our tables can be used to compare the intensities of different exercise studies.

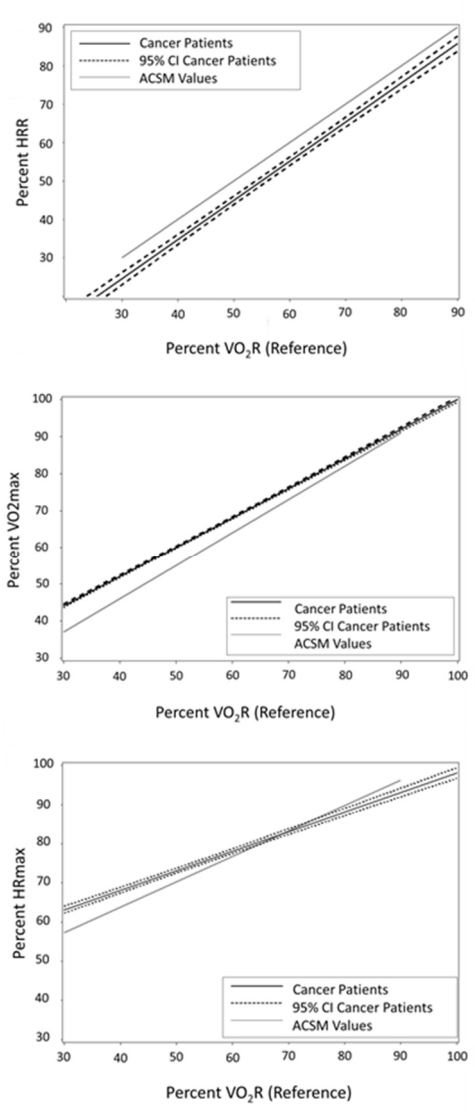

FIGURE 1. Observed and expected linear regression lines for VO_2R versus HRR, VO_2R versus VO_{2max}, and VO_2R versus HR_{max} before allo-HCT (*n*=106).

Since we observed different values for %HRR between the two time points without change in VO_{2max} and P_{max} values, our results also indicate that the relationship between HR and VO_2 may have changed after intensive treatment. Although the results of the paired t-tests did not reach significant levels, this change should be considered when prescribing exercise intensities.

Furthermore, we could not find an influence of beta-blockade on the %VO_2R and %HRR, %HR_{max} and %VO_{2max} relationship; therefore, we pooled data from patients with and without beta-blocker intake. This is consistent with other studies in heart disease patients which showed that the aforementioned relationships are not affected by beta-blockade (3, 24). Additionally, one study with healthy subjects showed that beta-blockade had no effect on VO_{2max} or P_{max} (39). This finding indicates that our intensity values can be applied to patients regardless of beta-blocker use, which is relevant since beta-blockers are frequently prescribed in cancer patients.

Despite having a large homogeneous sample, we observed a relatively large standard deviation for %HRR, indicating that there is some heterogeneity in the data. Our regression models revealed influence of hemoglobin levels, gender, BMI and age on the relationships, therefore these parameters may also be important to consider when defining intensity prescriptions; when using values estimated from the equation *220-age*, the variation was even larger. However, recommendations on individual level, for example using ventilatory thresholds (e.g. VT and respiratory compensation point), might be more useful for identifying the appropriate exercise intensity for an individual patient. When this is not possible, our values provided in the tables can be used instead. Additionally, we provide information about %P_{max} and %VT, because these parameters are also frequently used for prescribing exercise intensity in clinical practice. Our data show that %VO_{2max} did not correspond to %P_{max}, an important finding, since both are frequently used interchangeably in practice. Notably, in our patients VT occurred at 40% VO_{2max} which is lower than in untrained healthy people (23). VT was already suggested as an indicator for functional capacity in diseased patients when maximal incremental tests are not possible (23). However, our maximal CPET protocol was not ideal for cancer patients (see below) and therefore, these results should be interpreted with caution. Further studies should focus on determining whether VT as a submaximal parameter can be used to give adequate endurance training prescriptions for these patients. Additionally, prolonged exercise tests should be performed to further evaluate our recommended intensity values.

Our results are quite important from a clinical perspective, because first studies in hematological cancer patients after HCT show a potential relationship between cardiorespiratory fitness and survival (40), underlying the high importance of adequate exercise programs that target an optimal effect on cardiopulmonary fitness. Furthermore, our results underscore the need of individualized exercise prescriptions in this patient group. This finding complements with other results from our group showing that the individual exercise training response depends on baseline fitness level in allo-HCT patients (38).

One strength of our analysis is the large patient population. All patients received allo-HCT, an aggressive and demanding treatment which is known to profoundly impact physical performance. Furthermore, we included two measurement points to see if the relationship between HR and VO_2 change over time. Moreover, we used single linear regressions to calculate intensity categories. However, a methodological limitation is that our maximal CPET protocol started at a relatively high intensity (50W), therefore the lowest intensity class might be imprecisely represented, especially in patients with low physical performance. The assessment of resting VO_2 did not fulfill the criteria for resting measurement. However, Cunha et al. did not find a significant effect of different resting measurement conditions on the regression equation between VO_2R and HRR (9).

Conclusion

It becomes increasingly evident that maintaining cardiorespiratory fitness during cancer treatment and regaining fitness after treatment improves different outcomes, right up to survival. Despite a large body of evidence, accurate intensity recommendations regarding endurance training do not exist; instead, recommendations for healthy subjects are used. Our data show that this exercise intensity classification may not be valid in hematological cancer patients prior to and 180 days after allo-HCT because it may result in over- or underestimation of exercise intensity. We provide exercise intensity classifications that were derived from a large population of hematological cancer patients prior to and after allo-HCT. These classifications can be used to define more appropriate exercise prescriptions in hematological cancer patients and to compare intensities used in previous studies. Due to variability in the observed data, more research is needed to further evaluate optimal exercise intensities with respect to different treatment conditions in hematological cancer patients.

Funding: German José Carreras Leukemia Foundation (project no. R10/42pf)

Acknowledgements: The results of the present study do not constitute endorsement by the American College of Sports Medicine. The authors thank the study participants who spend their time, Andrea Bondong, Linda Keilbach, and Kristin Zerfass from the case management in the allogeneic transplantation ambulance at the University Clinic Heidelberg for recruitment and coordination assistance, the MTAs of the department of Sports Medicine at the University Clinic Heidelberg for assistance in CPET, and Michael Paskow for critically reading the manuscript.

Conflict of interest: none

REFERENCES

1. Baumann FT, Kraut L, Schule K, Bloch W, and Fauser AA. A controlled randomized study examining the effects of exercise therapy on patients undergoing haematopoietic stem cell transplantation. *Bone Marrow Transplant*. 2009;45(2):355-62.
2. Beaver WL, Wasserman K, and Whipp BJ. A new method for detecting anaerobic threshold by gas exchange. *J Appl Physiol*. 1986;60(6):2020-7.
3. Brawner CA, Keteyian SJ, and Ehrman JK. The relationship of heart rate reserve to VO2 reserve in patients with heart disease. *Med Sci Sports Exerc*. 2002;34(3):418-22.
4. Buffart LM, Galvao DA, Brug J, Chinapaw MJ, and Newton RU. Evidence-based physical activity guidelines for cancer survivors: current guidelines, knowledge gaps and future research directions. *Cancer Treat Rev*. 2014;40(2):327-40.
5. Byrne NM, and Hills A. Relationships between HR and (.)VO(2) in the obese. *Med Sci Sports Exerc*. 2002;34(9):1419-27.
6. Carlson LE, Smith D, Russell J, Fibich C, and Whittaker T. Individualized exercise program for the treatment of severe fatigue in patients after allogeneic hematopoietic stem-cell transplant: a pilot study. *Bone Marrow Transplant*. 2006;37(10):945-54.
7. Copelan EA. Hematopoietic stem-cell transplantation. *N Engl J Med*. 2006;354(17):1813-26.
8. Courneya KS, Sellar CM, Stevinson C, McNeely ML, Peddle CJ, Friedenreich CM, Tankel K, Basi S, Chua N, Mazurek A, and Reiman T. Randomized controlled trial of the effects of aerobic exercise on physical functioning and quality of life in lymphoma patients. *J Clin Oncol*. 2009;27(27):4605-12.
9. Cunha FA, Midgley AW, Monteiro WD, and Farinatti PT. Influence of cardiopulmonary exercise testing protocol and resting VO(2) assessment on %HR(max), %HRR, %VO(2max) and %VO(2)R relationships. *Int. J. Sports Med.* 2010;31(5):319-26.
10. da Cunha FA, Farinatti Pde T, and Midgley AW. Methodological and practical application issues in exercise prescription using the heart rate reserve and oxygen uptake reserve methods. *J Sci Med Sport*. 2011;14(1):46-57.
11. Dimeo F, Schwartz S, Fietz T, Wanjura T, Boning D, and Thiel E. Effects of endurance training on the physical performance of patients with hematological malignancies during chemotherapy. *Support Care Cancer*. 2003;11(10):623-8.

12. Elbl L, Vasova I, Tomaskova I, Jedlicka F, Kral Z, Navratil M, Smardova L, Wagnerova B, and Vorlicek J. Cardiopulmonary exercise testing in the evaluation of functional capacity after treatment of lymphomas in adults. *Leuk Lymphoma*. 2006;47(5):843-51.
13. Garber CE, Blissmer B, Deschenes MR, Franklin BA, Lamonte MJ, Lee IM, Nieman DC, Swain DP, and American College of Sports M. 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.
14. Hayes SC, Davies PS, Parker TW, Bashford J, and Green A. Role of a mixed type, moderate intensity exercise programme after peripheral blood stem cell transplantation. *Br J Sports Med*. 2004;38(3):304-9; discussion 9.
15. Hayes SC, Spence RR, Galvao DA, and Newton RU. Australian Association for Exercise and Sport Science position stand: optimising cancer outcomes through exercise. *J Sci Med Sport*. 2009;12(4):428-34.
16. Howley ET, Bassett DR, Jr., and Welch HG. Criteria for maximal oxygen uptake: review and commentary. *Med Sci Sports Exerc*. 1995;27(9):1292-301.
17. Jarden M, Baadsgaard MT, Hovgaard DJ, Boesen E, and 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.
18. Jones LW, Eves ND, Haykowsky M, Freedland SJ, and Mackey JR. Exercise intolerance in cancer and the role of exercise therapy to reverse dysfunction. *Lancet Oncol*. 2009;10(6):598-605.
19. Knols RH, de Bruin ED, Uebelhart D, Aufdemkampe G, Schanz U, Stenner-Liewen F, Hitz F, Taverna C, and Aaronson NK. 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.
20. Lakoski SG, Eves ND, Douglas PS, and Jones LW. Exercise rehabilitation in patients with cancer. *Nat Rev Clin Oncol*. 2012;9(5):288-96.
21. Lee HJ, Oran B, Saliba RM, Couriel DM, Shin K, Massey P, Neumann J, de Lima M, Champlin R, and Giralt S. Steroid myopathy in patients with acute graft-versus-host disease treated with high-dose steroid therapy. *Bone Marrow Transplant*. 2006;38(4):299-303.
22. Lounana J, Campion F, Noakes T, and Medello J. Relationship between %HRmax, %HR Reserve, %VO2max, and %VO2 Reserve in Elite Cyclists. *Med Sci Sports Exerc*. 2007;39:350-7.
23. Meyer T, Lucia A, Earnest CP, and Kindermann W. A conceptual framework for performance diagnosis and training prescription from submaximal gas exchange parameters--theory and application. *Int J Sports Med*. 2005;26 Suppl 1:S38-48.
24. Mezzani A, Corra U, Giordano A, Cafagna M, Adriano EP, and Giannuzzi P. Unreliability of the %VO2 reserve versus %heart rate reserve relationship for aerobic effort relative intensity assessment in chronic heart failure patients on or off beta-blocking therapy. *Eur J Cardiovasc Prev Rehabil*. 2007;14(1):92-8.
25. Midgley AW, McNaughton LR, Polman R, and Marchant D. Criteria for determination of maximal oxygen uptake: a brief critique and recommendations for future research. *Sports Med*. 2007;37(12):1019-28.
26. Persoon S, Kersten MJ, van der Weiden K, Buffart LM, Nollet F, Brug J, and Chinapaw MJ. Effects of exercise in patients treated with stem cell transplantation for a hematologic malignancy: a systematic review and meta-analysis. *Cancer Treat Rev*. 2013;39(6):682-90.
27. Schmitz KH, Courneya KS, Matthews C, Demark-Wahnefried W, Galvao DA, Pinto BM, Irwin ML, Wolin KY, Segal RJ, Lucia A, Schneider CM, von Gruenigen VE, and Schwartz AL. American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. *Med Sci Sports Exerc*. 2010;42(7):1409-26.
28. Shelton ML, Lee JQ, Morris GS, Massey PR, Kendall DG, Munsell MF, Anderson KO, Simmonds MJ, and Giralt SA. A randomized control trial of a supervised versus a self-directed exercise program for allogeneic stem cell transplant patients. *Psychooncology*. 2008;18(4):353-9.
29. Simmons DN, Berry MJ, Hayes SI, and Walschlager SA. The relationship between %HRpeak and %VO2peak in patients with chronic obstructive pulmonary disease. *Med Sci Sports Exerc*. 2000;32(5):881-6.
30. Steins Bisschop CN, Velthuis MJ, Wittink H, Kuiper K, Takken T, van der Meulen WJ, Lindeman E, Peeters PH, and May AM. Cardiopulmonary exercise testing in cancer rehabilitation: a systematic review. *Sports Med*. 2012;42(5):367-79.
31. Swain DP, Abernathy KS, Smith CS, Lee SJ, and Bunn SA. Target heart rates for the development of cardiorespiratory fitness. *Med Sci Sports Exerc*. 1994;26(1):112-6.
32. Swain DP, and Leutholtz BC. Heart rate reserve is equivalent to %VO2 reserve, not to %VO2max. *Med Sci Sports Exerc*. 1997;29(3):410-4.
33. White AC, Terrin N, Miller KB, and Ryan HF. Impaired respiratory and skeletal muscle strength in patients prior to hematopoietic stem-cell transplantation. *Chest*. 2005;128(1):145-52.
34. Wilson RW, Jacobsen PB, and Fields KK. Pilot study of a home-based aerobic exercise program for sedentary cancer survivors treated with hematopoietic stem cell transplantation. *Bone Marrow Transplant*. 2005;35(7):721-7.
35. Winters-Stone KM, Neil SE, and Campbell KL. Attention to principles of exercise training: a review of exercise studies for survivors of cancers other than breast. *Br J Sports Med*. 2014;48(12):987-95.
36. Wiskemann J, Dreger P, Schwerdtfeger R, Bondong A, Huber G, Kleindienst N, Ulrich CM, and Bohus M. Effects of a partly self-administered exercise program before, during, and after allogeneic stem cell transplantation. *Blood*. 2011;117(9):2604-13.
37. Wiskemann J, and Huber G. Physical exercise as adjuvant therapy for patients undergoing hematopoietic stem cell transplantation. *Bone Marrow Transplant*. 2008;41(4):321-9.
38. Wiskemann J, Kuehl R, Dreger P, Schwerdtfeger R, Huber G, Ulrich CM, Jaeger D, and Bohus M. Efficacy of exercise training in SCT patients-who benefits most? *Bone Marrow Transplant*. 2014;49(3):443-8.
39. Wonisch M, Hofmann P, Fruhwald FM, Kraxner W, Hodl R, Pokan R, and Klein W. Influence of beta-blocker use on percentage of target heart rate exercise prescription. *Eur J Cardiovasc Prev Rehabil*. 2003;10(4):296-301.
40. Wood WA, Deal AM, Reeve BB, Abernethy AP, Basch E, Mitchell SA, Shatten C, Hie Kim Y, Whitley J, Serody JS, Shea T, and Battaglini C. Cardiopulmonary fitness in patients undergoing hematopoietic SCT: a pilot study. *Bone Marrow Transplant*. 2013;48(10):1342-9.

5 Manuscript IV

Submitted to Medicine & Science in Sports & Exercise (MSSE)
Impact Factor: 4.48 (2013)
Submitted: 19 June 2015

Determinants of exercise adherence in cancer patients during and after allogeneic HCT

Kuehl, Rea[1,2] ; Schmidt, Martina E.[2]; Dreger, Peter[3]; Steindorf, Karen[2]; Bohus, Martin[4,5] ; Wiskemann, Joachim[1,2]

[1]Department of Medical Oncology, National Center for Tumor Diseases (NCT) and Heidelberg University Hospital, Germany
[2]Division of Preventive Oncology, National Center for Tumor Diseases (NCT) and German Cancer Research Center, 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

ABSTRACT

Objective: Evidence from randomized controlled trials is growing that exercise interventions are beneficial in cancer patients receiving allogeneic stem cell transplantation (allo-HCT). However, information about adherence to exercise interventions and exercise contamination in control groups is lacking. This information is crucial for the interpretation of study results. We therefore examined the determinants of exercise adherence and contamination in different treatment periods during (inpatient) and after (outpatient) allo-HCT.

Methods: One-hundred-fifty-three patients scheduled for allo-HCT were randomized to a one-year partly supervised exercise intervention (endurance and resistance exercise) or a control group (progressive muscle relaxation). Adherence was assessed via exercise logs and contamination via physical activity questionnaires.

Results: Adherence varied between 66% and 78% in different treatment periods. Linear regression models revealed that adherence during transplantation period (inpatient) was significantly influenced by fatigue (P=0.004), and having children at home (P=0.049). Adherence after discharge was influenced by endurance performance (P=0.003); adherence in the last outpatient phase was influenced by baseline exercise (P=0.010) and adherence after discharge (P=0.001). Contamination among controls was high with 54% and significantly associated with muscle strength (P=0.025) and physical fatigue (P=0.050).

Conclusions: Exercise adherence in different treatment periods was determined by different variables and contamination among controls was evident. These findings may have important implications for correct interpretation of randomized exercise intervention trials in cancer patients.

Keywords: physical activity, cancer, adherence, contamination, transplantation, oncology

INTRODUCTION

Allogeneic stem cell transplantation (allo-HCT) is a demanding treatment associated with severe side-effects, complications such as graft versus host disease (GvHD), and high mortality rates (2, 17, 21). There is a growing body of evidence suggesting that exercise interventions may be beneficial in reducing side-effects such as fatigue, maintaining physical function during treatment, enhancing physical fitness after treatment, and subsequently improving quality of life (18, 23, 25, 26). Additionally, our group published recently data showing a potential positive effect of exercise on prognosis after allo-HCT (27). General exercise guidelines for cancer survivors have been published (19), however, implementation of exercise programs during allo-HCT remains a unique challenge, and has been little investigated. In order to interpret the results of randomized exercise intervention trials (RCT), and to translate programs into clinical care, information on adherence to the investigated exercise program but also on contamination of the control group is important.

Exercise adherence is the degree to which a person fulfills a given exercise prescription (31). Efficacy of an exercise intervention can only be investigated when patients adhere to the prescribed program. Reporting of adherence is inconsistent due to heterogeneous definitions. For example, adherence has been described as number of exercise sessions attended, number of sessions completed, percentages of meeting exercise guidelines, or exercise minutes per week (11). It is suggested to report adherence to each of the FITT criteria (frequency, intensity, time and type of exercise) in order to demonstrate if patients were able to follow the exercise protocol, and to describe the exercise dose received (24). Further, it is still unclear whether adherence rates are different in different treatment phases (during vs. after treatment) and in supervised vs. home-based settings. A recent review revealed that 73% of all supervised studies in the transplant setting did not report adherence rates at all (9).

An equally important, but far less acknowledged problem of exercise RCTs is the contamination of the control group. Contamination refers to the extent to which the control group has adopted the intervention and started to exercise on their own. For example, a home-based walking intervention in breast cancer patients seemed to have no effect on fatigue, but further analyses revealed that 50% of control group (CG) subjects were exercising during the study period, and about 30% of exercise group (EG) subjects did not maintain the prescribed exercise program of 90 min walking per week. When the authors compared the high walking (more than 90 min/week) to the low walking (less than 90min/week) group they were still able to detect significant differences between groups (15). However, per-protocol analysis implicates a reverse causation problem.

Following the intention-to-treat principle of RCTs, poor adherence on one side and high contamination on the other side may diminish a potential true effect of the prescribed exercise intervention towards null (30). Furthermore, adherence and contamination are influenced by the enrolled population. A low recruitment rate in combination with a good retention might reflect the problem of recruiting a selective sample, likely over-representing subjects with generally better health, higher exercise-affinity, motivation or self-efficacy. However, patients with generally low health and feeling that they cannot carry out the exercise program may refuse to participate (9). This selection may limit generalizability of findings.

Therefore, we analyzed data from a large ongoing RCT (PETRA-Study) (28) in allo-HCT patients to gain a deeper insight into determinants of both, adherence and contamination, in in- and outpatient treatment phases. Understanding these data may help to develop more individualized exercise recommendations, achieve better adherence, consequently improving outcomes, and enhance interpretation of study results.

METHODS

Design and Participants

The PETRA study is a large ongoing RCT in 256 hematological cancer patients during and after allo-HCT with 2-year overall survival as primary outcome. The study design has been reported elsewhere (28). The study is registered at ClinicalTrials.gov (NCT01374399) and approved by the local ethic committees. Here, we analyzed the data of the first 153 patients included in the PETRA study.

Interventions

Briefly, patients assigned to the EG started the one-year intervention program (endurance and resistance exercise, 3-5x/week) at the first day of conditioning for allo-HCT (chemotherapy, total body irradiation) in isolation units at the hospital. During this first period three of the weekly sessions were supervised. After hospital discharge patients continued the exercise program home-based (3-5x/week) and were called regularly per phone to check on their adherence. The exercise program was individually adapted and tailored, based on the intervention program evaluated in our previous RCT (25). Motivational working packages were

included to enhance adherence. Contraindications for exercise were low thrombocyte counts (< 15µl), infections/ fever, and dizziness.

Patients assigned to the CG received a muscle relaxation program (according to Jacobson) (1) with three supervised sessions per week during inpatient stay, and continued the program home-based, including regular phone calls.

Measurements

Assessment points for this analysis were prior allo-HCT, at the day of discharge, 100 days and 180 days after allo-HCT (see figure 1). To assess adherence, patients in the EG filled out exercise logs at each training day. In these logs patients could fill in the total exercise duration per day, what type of exercise they performed (endurance, resistance, or both), and whether they had to stop exercise prematurely due to specific reasons, e.g. fatigue, nausea or lack of motivation, or record why they could not perform the program (only after day 100). Patients were also asked to document exercise activities carried out during additional supportive care programs (e.g. physiotherapy, rehabilitation) in the exercise log. During supervised exercise sessions, the study personnel documented reasons if exercise could not be performed due to medical contraindications. Exercise logs were returned at each assessment time point.

To evaluate exercise contamination in the CG at 180 days after transplantation, patients were asked to self-report the amount of physical activity in a typical week since the last assessment via questionnaire.

Details of our physical performance assessment procedures and patient-reported outcomes (PROs) were described elsewhere (28). Briefly, we assessed physical performance with the 6-minute walk test (6MWT), and isometric muscle strength with a hand-held dynamometer. For PROs we used standardized questionnaires (MFI, EORTC QLQ). Baseline characteristics were assessed via questionnaires and medical chart reviews, and incidence and severity of GvHD were documented by attending physicians.

Statistical analysis

Baseline characteristics and other group characteristics were compared using t-tests for continuous data and Chi-square test or Fisher's exact test for categorical data. Adherence was calculated for each intervention period as total minutes of exercise in this period divided by the period length (in weeks), i.e. min/week. For contamination we calculated total hours of walking, sport-activities and cycling per week, based on our questionnaire at the time point 180 days after allo-HCT. Linear regression models were calculated with adherence and contamination as dependent variables and potentially relevant factors, assessed at baseline and at each measurement point as independent variables, including: (1) demographic and medical data: age, gender, education (4 categories), family history, time since diagnosis, and development of GvHD larger than grade 1; (2) health-related fitness variables: body-mass-index (BMI), submaximal endurance capacity (walking distance), knee-extensor muscle strength, physical activity (walking, cycling, sport-activities) at baseline and during adolescence (sport-activity); and (3) PROs: general and physical fatigue (MFI), different quality of life domains, e.g. physical functioning, role functioning, and general quality of life (EORTC). In consideration of multicollinearity, we aimed to identify the most relevant determinants. To explore the stability of the results, several a priori plausible sets of covariates were calculated. Variables that neither showed significant associations with the dependent variable nor had confounding effects on other covariates were dropped from the final model (13). For each study period a separate model for adherence was calculated. We log-transformed the dependent variables adherence to fulfill the normality assumption of residues. As a secondary sensitivity analysis, for regression models, missing adherence values were imputed using information obtained during regular phone calls. Reported p-values are two-sided with significant level of 0.05. SAS statistical software version 9.3 (SAS Institute, Cary, NC, USA) was used.

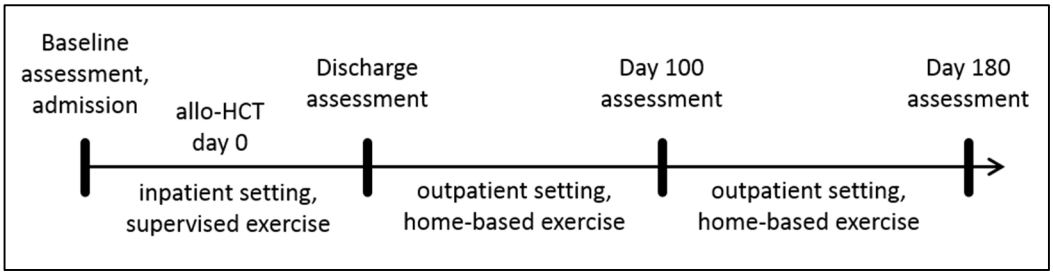

FIGURE 1. Observed intervention periods.

RESULTS

Recruitment and retention

Recruitment took place from February 2011 until November 2013 (see figure 2), and 153 patients were randomized at the day of admission. Baseline characteristics of the study population are described in table 1. Since the study is still ongoing, 12 patients had not yet reached the 180 day measurement at the time of data analysis. Primary reasons for drop-out were no interest in muscle relaxation (CG), and feeling to be too overburdened to perform the physical tests.

Adherence to the exercise intervention

Adherence data for three different study periods are presented in table 2, based on the returned logs. Main reasons for not exercising during the first study period were fever, low thrombocyte counts and severe side-effects from conditioning therapy (inpatient setting during transplantation process, isolation rooms).

Determinants for exercise adherence

Determinants for higher adherence during inpatient stay were low physical fatigue (MFI, P=0.004), and having children at home (P=0.049). Determinant for a higher adherence after discharge up to day 100 was a better submaximal endurance performance at discharge (6 MWT, P=0.003), when controlling for emotional functioning (P=0.189). For adherence between day 100 up to day 180 significant determinants were sport-activity at baseline (P=0.010) and higher exercise adherence after discharge (P=0.001). The models for the three time points explained 16%, 21% and 55% of variance, respectively (table 3). Variables not listed in the table (e.g. demographics and medical data) showed no significant associations with adherence, neither in the univariate nor in the multivariate adjusted models. When using the imputed adherence variables, no significant changes in determinants were observed.

Contamination of control group

One-hundred-eighty days after allo-HCT, 26 patients (54.2 %) of the CG stated that they were currently doing some kind of sport-activity, and 43 patients (89.6 %) stated that they were walking on a regular basis. Time spent walking was on median 4.0 (interquartile range: 2.0-7.5) hours per week. Only 5 patients (22.9%) of the CG reported no activity at all. Eleven CG patients (23.9%) received outpatient physiotherapy, 5 patients (10.9%) received inpatient rehabilitation, and one patient (2.2%) outpatient rehabilitation. For comparison, in the EG 10 patients (20%), 3 patients (6%) and 2 patients (4%) received these additional support activities, respectively.

Determinants for contamination

Determinants for contamination were higher isometric muscle strength (P=0.025) and lower physical fatigue (P=0.050) 180 days after transplantation. Total variance that could be explained was 29.4% (P=0.001). The model is presented in table 4.

DISCUSSION

To our knowledge, this is the first study that examined the determinants of exercise adherence and contamination in an RCT in the transplantation setting. We could define different determinants for adherence in different treatment phases. Adherence to inpatient exercise was better among patients having children at home and lower fatigue, whereas sport-activity before transplantation, and higher endurance performance and high adherence directly after discharge were significant determinants for higher adherence in the outpatient home-based settings. Significant determinants for contamination among controls were high isometric muscle strength and low physical fatigue.

In order to translate exercise programs into clinical practice it is crucial to give detailed information about adherence and to demonstrate that the prescribed exercise intervention could be performed by the individual patient. A recent review summarized, that the majority of all supervised studies in the transplant setting did not report adherence data (9). Regarding allo-HCT patients only, three RCTs reported adherence rates: The first study by Jarden et al. was conducted during hospital stay for allo-HCT (4-6 weeks) and they reported 90% adherence (defined as attendance) to their five times per week supervised multimodal exercise program (10). Another study in 100 allo-HCT patients examining a daily unsupervised walking intervention (30 min) during and after allo-HCT reported an adherence rate of only 24% (7). In comparison, in a previous RCT conducted by our group we received adherence rates of 83 to 91% prior, during and after treatment (25).

Since our observed intervention period in this study was relatively long and took place in different clinical settings, we looked at exercise adherence during the inpatient period, the outpatient periods till day 100 and till day 180 after allo-HCT separately. With regard to exercise adherence, 66 to 78% of all patients were able to exercise more than three times per week, and exercise duration increased from 89 to 199 min during the entire studied period. As expected, during inpatient period exercise frequency and duration was lowest,

TABLE 1: Baseline characteristic of study population

		Exercise group		Control group		*P*
TOTAL n,%		76	100%	77	100%	
Age, mean (SD)		53.4	(10.1)	54.2	(11.7)	
Gender, n %	female	24	31.6%	26	33.8%	
	male	52	68.4%	51	66.2%	
BMI, mean (SD)		26.6	(4.5)	25.7	(4.6)	
Married, n %	no	5	6.6%	7	9.1%	
	yes	71	93.4%	70	90.9%	
Level of education, n %	low	16	21.1%	15	19.5%	
	medium	23	30.3%	12	15.6%	<0.001*
	high	17	22.4%	25	32.5%	
	academic	19	25.0%	25	32.5%	
	miss	1	1.3%	0	0%	
Children at home, n %	yes	56	73.7%	53	68.8%	
	no	19	25.0%	21	27.3%	
	missing	1	1.3%	3	3.9%	
Any sports currently, n %	no	53	69.7%	49	63.6%	
	yes	23	30.3%	28	36.4%	
Walking regularly currently, n %	no	15	19.7%	14	18.2%	
	yes	61	80.3%	63	81.8%	
Walking h/week, currently, mean (SD)		3.5	(6.7)	3.4	(3.1)	
Cycling regularly currently, n %	no	59	77.6%	51	66.2%	
	yes	17	22.4%	26	33.8%	
Sports in childhood, n %	no sports	25	32.9%	19	24.7%	
	any sports	24	31.6%	28	36.4%	
	competitive	27	35.5%	30	39.0%	
Current smoking, n %	no	69	90.8%	72	93.5%	
	yes	4	5.3%	5	6.5%	
	missing	3	3.9%	0	0%	
Karnofsky Performance Score, median (Q1, Q3)		90.0	(90.0, 100.0)	90.0	(90.0, 100.0)	
Time since diagnosis, median (Q1,Q3)		11.9	(5.4, 42.8)	15.6	(4.8, 59.4)	
Complete remission, n %	no	45	59.2%	41	53.2%	
	yes	29	38.2%	33	42.9%	
	missing	2	2.6%	3	3.9%	
Diagnosis						
AML		20	13.0%	25	16.4%	
ALL		4	2.6%	5	3.3%	
Lymphoma/CLL		28	18.3%	26	16.9%	
MDS		11	7.2%	8	5.1%	
CML/MPS		2	1.3%	3	1.9%	
Multiple Myeloma		9	5.9%	9	5.9%	
Other		2	1.3%	0	0%	
Aplastic Syndrome		0	0%	1	0.6%	
Previous allo-HCT, n %		4	5.3%	3	3.9%	
Previous auto-HCT, n %		18	23.7%	14	18.2%	

BMI, body mass index; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; CLL, chronic lymphocytic leukemia; MDS, myelodysplastic syndrome; CML, chronic myeloid leukemia; MPS, myeloproliferatory syndrome; allo-HCT, allogeneic hematopoietic stem cell transplantation; auto-HCT, autologous hematopoietic stem cell transplantation

*Chi2-test, only significant (P>0.05) P-values listed

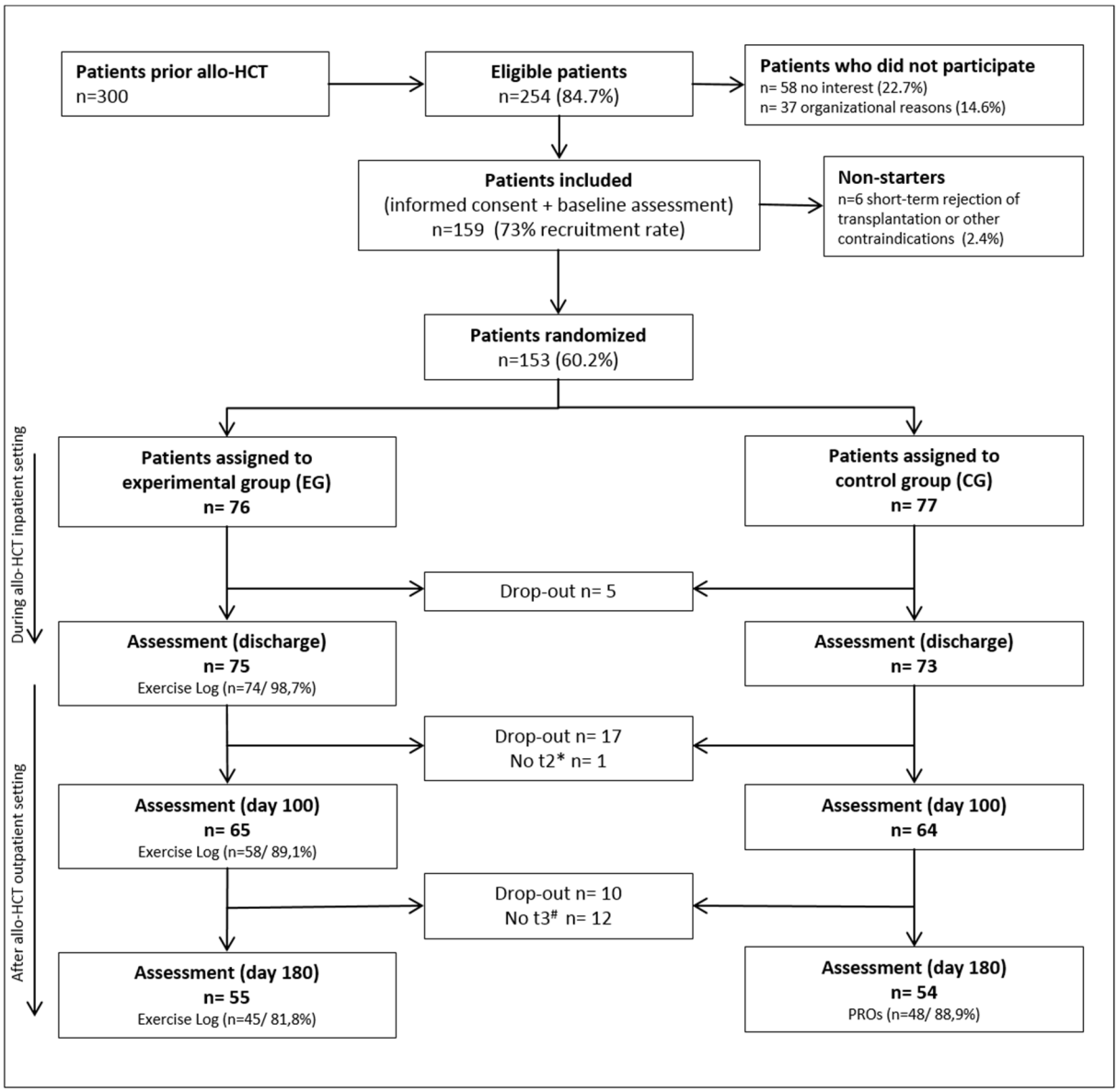

FIGURE 2. Patient flow chart showing the numbers of patients who were recruited and randomized and run through the assessment points.

noticing, that this period includes the phase of severe side-effects contraindicating exercise. General exercise guidelines for cancer survivors recommend 150 min moderate activity per week (19). After discharge 40%, and after day 100 60% of patients in the exercise group reached this recommendation. We observed, however, a large variation in exercise duration between patients.

Due to the fact that most studies reported frequencies of sessions attended, the actual volume or dose of exercise performed remained unclear. However, exact information is necessary to determine a possible dose-response effect. Therefore, we presented additional data on exercise duration. Furthermore, to gain a better understanding of poor adherence, the reasons for a premature stopping of the exercise sessions were considered. Interestingly, fatigue was in all phases the most frequent reason why exercise was terminated. High level of baseline fatigue was also significantly associated with low adherence during inpatient stay, and a significant determinant for low exercise contamination 180 days after allo-HCT.

Our data provided a unique possibility to study determinants of adherence in the course of different periods and settings. We found that less fatigue, higher endurance performance, sport-activity before transplantation and high adherence directly after

TABLE 2: Adherence in different study periods

	Inpatient		Outpatient ≤ day100		Outpatient > day100	
TOTAL patients*, n,%	74	100%	58	100%	45	100%
Training days/week, median (Q1, Q3)	3.5	(2.6, 4.2)	3.4	(2.8, 4.8)	4.3	(3.5, 5.2)
Strength training	1.2	(0.7, 1.6)	1.6	(0.9, 2.2)	0.9	(0.4, 1.5)
Aerobic training	0.8	(0.5, 1.3)	0.9	(0.5, 1.6)	2.0	(1.4, 2.9)
Mixed training	1.0	(0.4, 1.8)	0.5	(0.2, 1.3)	0.5	(0.2, 1.3)
Training on more than 3 days/ week, n,%	49	66.2%	38	65.4%	35	77.8%
Duration minutes/week, mean (SD)	89.2	(51.2)	147.6	(99.4)	198.8	(107.3)
Meeting exercise guidelines (150 min/ week), n,%	5	6.8%	23	39.7%	27	60.0%
Percentage of incomplete sessions**, median (Q1, Q3)	12.9	(0.0, 24.0)	8.8	(1.5, 23.8)	-	-
Reported reasons***:						
Fatigue		63.7%		44.8%		31.3%
Nausea		18.8%		8.2%		11.1%
Pain		14.8%		27.9%		15.1%
Lack of motivation		9.9%		8.7%		11.7%
Time constraints		-		2.6%		9.4%
Others		18.4%		15.6%		44.3%

* Data presented are based on the returned logs

** Only recorded in the first two periods

*** In the last period reasons for not exercising were reported. In the other periods reasons for exercise termination were reported

discharge were significant determinants for higher adherence in different treatment periods. The models explained 16%, 21% and 55% of variance respectively. These results are in line with a current review about determinants of adherence in other cancer populations. The authors reported moderate evidence for exercise history as consistent determinant, whereas other variables e.g. age, gender, fitness, education and psychological variables, yielded inconsistent results. They concluded that still little is known about determinants of adherence in different treatment phases and various settings (11). In a study in lymphoma patients, past exercise was also observed as significant predictor of adherence (6). Remarkably, GvHD, known as major complication after allo-HCT (8), and having profound impact on physical function (14), did not show to influence adherence in our study. This is in contrast to a retrospective trial where only 54% of patients with GvHD could adhere to a supervised exercise program (16). This result illustrates the challenging patient group and the need to individually adapt exercise programs.

A large proportion of the control group adopted exercise during the study. 89% of control group patients stated 180 days after allo-HCT that they were walking on a regular basis, 54% stated that they were doing some kind of sport-activity. Only few studies reported data on contamination and since results have been very inconsistent, a possible blurring effect of exercise contamination on the results of published RCTs is unknown. In the transplant setting only one RCT reported contamination, which was with 7.5% much lower than in our study (12). Comparable to our setting, an RCT in colorectal cancer survivors post-treatment examining a home-based walking program, reported a contamination rate of 52% (3), whereas another home-based mixed exercise program during active treatment in a mixed cancer population (mainly breast and prostate cancer) reported a contamination rate of only 12% (20). A possible explanation for contamination in our study could be the growing awareness of patients, clinicians and physiotherapists of the benefits of exercise after HCT. The positive results of our previous RCT (25, 29), conducted in the same hospital, might have further raised the knowledge among the clinical personnel regarding exercise during and after allo-HCT. We feel that the encouragement by physicians to engage in physical activity has increased substantially, and patients proactively ask for advice. Important to note, the control group had a significantly higher education level, which is known to lead to higher physical activity levels after cancer diagnosis (22). Significant determinants for contamination, i.e. for high activity 180 days after allo-HCT, were high isometric muscle strength and low physical fatigue, which explained 29% of variance. Comparing our results to other studies is complicated due to the fact that different predictors were included. For example, in the previously mentioned study with colorectal cancer survivors, intention and baseline

TABLE 3a: Significant associations between exercise adherence (exercise duration) during inpatient stay and demographic, medical, health-related fitness, and patient reported outcome variables.

Included Variables										
Univariate models*				**Multivariate model**				**Final multivariate model**		
	β	**R^2**	***P***		**β**	**R^2**	***P***		**β**	**R^2**	***P***
						23.1%	0.010			16%	0.003
Kids at home		4.7%	0.066	Kids at home			0.071	Kids at home			0.049
yes	ref.			yes	ref.			yes	ref.		
no	-0.33			no	-0.32			no	- 0.34		
Sport activity in adolescence		10.3%	0.024	Sport activity in adolescence			0.102				
no sports	ref.			no sports	ref.						
competitive	0.17			competitive	0.13						
any sports	0.40			any sports	0.32						
Cognitive functioning**	0.01	6%	0.036	Cognitive functioning**	0.01		0.538				
Physical fatigue (MFI)**	-0.04	10.9%	0.004	Physical fatigue (MFI)**	-0.05		0.075	Physical fatigue**	-0.04		0.004
General fatigue (MFI)**	-0.03	6.2%	0.040	General fatigue (MFI)**	0.02		0.400				

*only significant Variables listed; ** at baseline (admission); depended variable (adherence) log transformed

TABLE 3b: Significant associations between exercise adherence (exercise duration) after discharge up to day 100 and demographic, medical, health-related fitness, and patient reported outcome variables.

Included Variables										
Univariate models*				**Multivariate model**				**Final multivariate model**			
	β	**R^2**	***P***		**β**	**R^2**	***P***		**β**	**R^2**	***P***
						32.1%	0.020			21.2%	0.003
Kids at home		4.9%	0.099	Kids at home			0.393				
yes	ref.			yes	ref.						
no	-0.54			no	-0.25						
Family status		15.3%	0.030	Family status			0.215				
Single	ref.			Single	ref.						
Married	0.08			Married	-0.03						
Separated	-2.21			Separated	-1.46						
divorced	-0.41			divorced	-0.57						
Submaximal endurance capacity**	0.01	15.5%	0.002	Submaximal endurance capacity**	0.01		0.083	Submaximal endurance capacity**	0.01		0.003
Fatigue (EORTC)**	-0.01	8.2%	0.030	Fatigue (EORTC)**	0.01		0.483				
Emotional functioning**	0.01	9.5%	0.021	Emotional functioning**	0.01		0.379	Emotional functioning**	0.01		0.189#
Social functioning**	0.01	8.4%	0.031	Social functioning**	0.01		0.345				

*only significant variables listed; ** at discharge; #included because of better explained variance; depended variable (adherence) log transformed

TABLE 3c: Significant associations between exercise adherence (exercise duration) after day 100 up to day 180 and demographic, medical, health-related fitness, and patient reported outcome variables.

Included Variables										
Univariate models*				**Multivariate model**				**Final multivariate model**		
	β	**R^2**	***P***		**β**	**R^2**	***P***		**β**	**R^2**	***P***
						59.6%	0.001			55.4%	0.001
Exercise activity prior allo-HCT		13.2%	0.016	Exercise activity prior allo-HCT			0.004	Exercise activity prior allo-HCT			0.010
yes	ref.			yes	ref.			yes	ref.		
no	-0.42			no	-0.41			no	-0.33		
Submaximal endurance capacity**	0.01	13.5%	0.013	Submaximal endurance capacity**	-0.01		0.394				
Physical functioning**	0.01	8%	0.073	Physical functioning**	-0.01		0.745				
General fatigue (MFI)**	-0.04	7.7%	0.079	General fatigue (MFI)**	0.02		0.434				
Adherence after discharge	0.01	47.3%	0.001	Adherence after discharge	0.01		0.001	Adherence after discharge	0.01		0.001

*only significant variables listed; ** at day 100; depended variable (adherence) log transformed

TABLE 4: Significant associations between contamination in the control group (duration of walking, exercise, cycling) day 180 and demographic, medical, health-related fitness, and patient reported outcome variables.

Included Variables										
Univariate models*				**Multivariate model**				**Final multivariate model**			
	β	**R^2**	***P***		**β**	**R^2**	***P***		**β**	**R^2**	***P***
						35.8%	0.075			29.4%	0.001
Submaximal endurance capacity**	0.09	8%	0.059	Submaximal endurance capacity**	0.01		0.271				
Isometric muscle strength**	0.04	23.3%	0.001	Isometric muscle strength**	0.02		0.153	Isometric muscle strength**	0.03		0.025
Global quality of life**	0.09	15.1%	0.007	Global quality of life**	-0.02		0.696				
Fatigue (EORTC)**	-0.08	12.9%	0.014	Fatigue (EORTC)**	0.13		0.165				
Emotional functioning**	0.07	7.3%	0.066	Emotional functioning**	-0.01		0.950				
Role functioning**	0.09	21.3%	0.001	Role functioning**	0.06		0.255				
Physical functioning**	0.11	20.5%	0.002	Physical functioning**	0.01		0.895				
Physical fatigue (MFI)**	-0.60	21.3%	0.001	Physical fatigue (MFI)**	-0.14		0.706	Physical fatigue (MFI)**	-0.38		0.050
General fatigue (MFI)**	-0.64	17.1%	0.005	General fatigue (MFI)**	-0.64		0.158				

*only significant variables listed; ** at day 180

exercise stage of change (driven from the trans-theoretical model) were significant predictors for exercise contamination. However, demographics, past exercise, fitness, and medical variables had no influence (4). Conversely, in the second mentioned study past exercise history was the only significant predictor (20). Likely, the contamination of the control group depends on the setting and type of intervention.

Detailed information about recruitment rates are rarely reported in the setting of hematological cancer patients. In contrast to our relatively high recruitment rate of 73%, other studies included 25 to 91% of eligible patients (5, 10, 12). Since the main intervention mode of the PETRA study is a home-based program, and the intervention duration (one year) is quite long, we think that recruitment works well and provides a representative sample of the underlying population.

Strengths of our study comprise a large representative sample and long intervention duration, including different treatment periods. Furthermore, this is the first study that examined adherence during inpatient and outpatient setting in more detail, and investigated determinants for adherence and contamination in the transplant setting. However, it should be noted that there are limitations to this study. Adherence and physical activity were assessed via self-report; therefore over- or underreporting might have biased our results. Also, we have only data of physical activity (contamination) 180 days after transplantation. Data on type of disease, previous treatment modalities and intensity of conditioning chemotherapy prior allo-HCT were not considered as determinants in the models. However, we included time since diagnosis as a predictor variable.

In summary, the exercise adherence rate was between 66 and 77% in the different periods, and we were able to identify various determinants for adherence in the three studied intervention periods. Whereas fatigue was an important predictor for adherence during inpatient setting, physical performance and physical activity before transplantation were determinants for the adherence in the home-based settings. These are important information when translating exercise programs into clinical practice. Future research should focus on improving adherence in patients who have problems to adopt regular exercise, thus optimizing individually tailored programs. However, contamination of the control group is a substantial issue and should be considered in all ongoing and future exercise trials.

Funding: Deutsche José Carreras Leukämie Stiftung e.V. (project no. R10/42pf)

The results of the present study do not constitute endorsement by the American College of Sports Medicine.

Conflict of interest: none

References

1. Bernstein D, and Borkovec T. Progressive relaxation training: A manual for the helping profession. *Champaign, IL: Research Press*. 1973.
2. Copelan EA. Hematopoietic stem-cell transplantation. *N Engl J Med*. 2006;354(17):1813-26.
3. Courneya KS, Friedenreich CM, Quinney HA, Fields AL, Jones LW, and Fairey AS. A randomized trial of exercise and quality of life in colorectal cancer survivors. *Eur J Cancer Care (Engl)*. 2003;12(4):347-57.
4. Courneya KS, Friedenreich CM, Quinney HA, Fields AL, Jones LW, and Fairey AS. Predictors of adherence and contamination in a randomized trial of exercise in colorectal cancer survivors. *Psychooncology*. 2004;13(12):857-66.
5. Courneya KS, Sellar CM, Stevinson C, McNeely ML, Peddle CJ, Friedenreich CM, Tankel K, Basi S, Chua N, Mazurek A, and Reiman T. Randomized controlled trial of the effects of aerobic exercise on physical functioning and quality of life in lymphoma patients. *J Clin Oncol*. 2009;27(27):4605-12.
6. Courneya KS, Stevinson C, McNeely ML, Sellar CM, Peddle CJ, Friedenreich CM, Mazurek A, Chua N, Tankel K, Basi S, and Reiman T. Predictors of adherence to supervised exercise in lymphoma patients participating in a randomized controlled trial. *Ann Behav Med*. 2010;40(1):30-9.
7. DeFor T, Burns L, Gold E, and 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.
8. Ferrara JL, Levine JE, Reddy P, and Holler E. Graft-versus-host disease. *Lancet*. 2009;373(9674):1550-61.
9. Hacker ED, and Mjukian M. Review of attrition and adherence in exercise studies following hematopoietic stem cell transplantation. *Eur J Oncol Nurs*. 2014;18(2):175-82.
10. Jarden M, Baadsgaard MT, Hovgaard DJ, Boesen E, and 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.
11. Kampshoff CS, Jansen F, van Mechelen W, May AM, Brug J, Chinapaw MJ, and Buffart LM. Determinants of exercise adherence and maintenance among cancer survivors: a systematic review. *Int J Behav Nutr Phys Act*. 2014;11(1):80.
12. Knols RH, de Bruin ED, Uebelhart D, Aufdemkampe G, Schanz U, Stenner-Liewen F, Hitz F, Taverna C, and Aaronson NK. 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.
13. Kuehl R, Scharhag-Rosenberger F, Schommer K, Schmidt ME, Dreger P, Huber G, Bohus M, Ulrich CM, and Wiskemann J. Exercise Intensity Classification in

Cancer Patients Undergoing Allogeneic HCT. *Med Sci Sports Exerc*. 2015;47(5):889-95.
14. Mitchell SA, Leidy NK, Mooney KH, Dudley WN, Beck SL, LaStayo PC, Cowen EW, Palit P, Comis LE, Krumlauf MC, Avila DN, Atlam N, Fowler DH, and Pavletic SZ. Determinants of functional performance in long-term survivors of allogeneic hematopoietic stem cell transplantation with chronic graft-versus-host disease (cGVHD). *Bone Marrow Transplant*. 2010;45(4):762-9.
15. Mock V, Pickett M, Ropka ME, Muscari Lin E, Stewart KJ, Rhodes VA, McDaniel R, Grimm PM, Krumm S, and McCorkle R. Fatigue and quality of life outcomes of exercise during cancer treatment. *Cancer Pract*. 2001;9(3):119-27.
16. Morris GS, Brueilly KE, Scheetz JS, and 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.
17. Passweg JR, Baldomero H, Bregni M, Cesaro S, Dreger P, Duarte RF, Falkenburg JH, Kroger N, Farge-Bancel D, Bobby Gaspar H, Marsh J, Mohty M, Peters C, Sureda A, Velardi A, Ruiz de Elvira C, and Madrigal A. Hematopoietic SCT in Europe: data and trends in 2011. *Bone Marrow Transplant*. 2013;48(9):1161-7.
18. Persoon S, Kersten MJ, van der Weiden K, Buffart LM, Nollet F, Brug J, and Chinapaw MJ. Effects of exercise in patients treated with stem cell transplantation for a hematologic malignancy: a systematic review and meta-analysis. *Cancer Treat Rev*. 2013;39(6):682-90.
19. Schmitz KH, Courneya KS, Matthews C, Demark-Wahnefried W, Galvao DA, Pinto BM, Irwin ML, Wolin KY, Segal RJ, Lucia A, Schneider CM, von Gruenigen VE, and Schwartz AL. American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. *Med Sci Sports Exerc*. 2010;42(7):1409-26.
20. Shang J, Wenzel J, Krumm S, Griffith K, and Stewart K. Who will drop out and who will drop in, exercise adherence in a randomized clinical trial among patients receiving active cancer treatment. *Cancer Nurs*. 2012;35(4):312-22.
21. Sorror ML, Storer BE, Maloney DG, Sandmaier BM, Martin PJ, and Storb R. Outcomes after allogeneic hematopoietic cell transplantation with nonmyeloablative or myeloablative conditioning regimens for treatment of lymphoma and chronic lymphocytic leukemia. *Blood*. 2008;111(1):446-52.
22. Stevinson C, Tonkin K, Capstick V, Schepansky A, Ladha AB, Valance JK, Faught W, Steed H, and Courneya KS. A population-based study of the determinants of physical activity in ovarian cancer survivors. *J Phys Act Health*. 2009;6(3):339-46.
23. van Haren IE, Timmerman H, Potting CM, Blijlevens NM, Staal JB, and Nijhuis-van der Sanden MW. Physical exercise for patients undergoing hematopoietic stem cell transplantation: systematic review and meta-analyses of randomized controlled trials. *Phys Ther*. 2013;93(4):514-28.
24. Winters-Stone KM, Neil SE, and Campbell KL. Attention to principles of exercise training: a review of exercise studies for survivors of cancers other than breast. *Br J Sports Med*. 2014;48(12):987-95.
25. Wiskemann J, Dreger P, Schwerdtfeger R, Bondong A, Huber G, Kleindienst N, Ulrich CM, and Bohus M. Effects of a partly self-administered exercise program before, during, and after allogeneic stem cell transplantation. *Blood*. 2011;117(9):2604-13.
26. Wiskemann J, and Huber G. Physical exercise as adjuvant therapy for patients undergoing hematopoietic stem cell transplantation. *Bone Marrow Transplant*. 2008;41(4):321-9.
27. Wiskemann J, Kleindienst N, Kuehl R, Dreger P, Schwerdtfeger R, and Bohus M. Effects of physical exercise on survival after allogeneic stem cell transplantation. *Int J Cancer*. 2015.
28. Wiskemann J, Kuehl R, Dreger P, Huber G, Kleindienst N, Ulrich CM, and Bohus M. 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;(submitted).
29. Wiskemann J, Kuehl R, Dreger P, Schwerdtfeger R, Huber G, Ulrich CM, Jaeger D, and Bohus M. Efficacy of exercise training in SCT patients-who benefits most? *Bone Marrow Transplant*. 2014;49(3):443-8.
30. Woodard CM, and Berry MJ. Enhancing adherence to prescribed exercise: structured behavioral interventions in clinical exercise programs. *J Cardiopulm Rehabil*. 2001;21(4):201-9.
31. World Health Organisation (WHO) *Adherence to long-term therapies: Evidence for action*. Switzerland: WHO Library Cataloguing-in-Publication Data; 2003.

6 General Discussion

This thesis provides results from two large RCTs in hematological cancer patients during and after allo-HCT. The aim of this work was to enhance exercise prescriptions in allo-HCT patients and to give practical guidelines for designing exercise interventions and future interpretation of study findings.

This chapter summarizes the main findings and discusses the results in the light of the existing literature and methodological aspects. The chapter ends with clinical implications and suggestions for future research.

6.1 Summary Main Findings

In the first manuscript (chapter 2), we examined the impact of baseline physical performance on exercise response in the experimental group of the first RCT. When comparing the changes in physical performance of initially *fit* classified patients to *unfit* classified patients, we observed a significantly different development in both patient groups. Whereas the initially *fit* patients lost 31% of their strength of the knee-extensors, the *unfit* patients lost only 1% ($p<.01$). For endurance capacity, the initially *fit* patients lost 4%, whereas the *unfit* patients gained 13% ($p<.05$). The individual percent change was significantly different for all measures of physical performance. We concluded that initially *unfit* patients can exercise safely and may benefit more from exercise during and directly after allo-HCT than initially *fit* patients. This finding is of major clinical relevance because exercise is often not recommended in patients with poor health status and in deconditioned individuals. However, it might be that initially *fit* patients need a more intense exercise recommendation.

In the second manuscript (chapter 3), we described the rationale and the study design and all study procedures of our ongoing RCT called PETRA study. The PETRA study is a large exercise intervention trial during and up to one year after allo-HCT and will include 256 patients. The primary endpoint is overall survival after two years; secondary endpoints include for example physical performance, body composition, fatigue, quality of life, depression, distress, severity of side-effects, e.g. GvHD, effect on hematological and immunological reconstitution and inflammatory parameters. The experimental group performs a combined moderate intensity program consisting of endurance and resistance exercises, which is partly supervised during inpatient stays and self-directed home-based during outpatient stays. The control group receives a comparable program, but with progressive muscle relaxation to reduce social bias. The strengths of the study are the large sample size, the comprehensive assessment procedures, including gold-standard assessment procedures for assessing physical performance, and the intervention for the control group. This study provides a large data base to examine not only the effects on primary and secondary endpoints, but will give answers to highly important questions regarding optimizing exercise

interventions and exercise prescriptions in cancer patients. The two following manuscripts are based on data of the PETRA study.

In the third manuscript (chapter 4), we examined maximal cardiopulmonary exercise test (CPET) data of 106 PETRA patients prior to and 180 days after allo-HCT. We evaluated the relationship between $\%VO_{2reserve}$ and %HRR, $\%HR_{max}$ and $\%VO_{2max}$, and compared calculated endurance training intensities to given data from the ACSM in order to examine, if the currently used prescription from the ACSM is valid in allo-HCT patients. We observed that the ACSM's exercise intensity recommendations for endurance training might not meet the targeted intensity classes, with the exception of %HRR 180 days after allo-HCT, resulting in over- or under-estimation of exercise intensity. In addition, we provided a table with exercise intensity classes obtained in hematological cancer patients that can be used to give exercise prescriptions, and to compare intensities of other studies. Furthermore, we found out that applying exercise intensity recommendations based on percentages of the commonly used equation *220-age* also did not provide appropriate intensities. This was the first study that compared the widely used ACSM intensity prescriptions with a population of cancer patients.

In the last manuscript (chapter 5), we proved that our recruitment of the first 153 patients in the PETRA study was excellent (73%), providing us with a representative sample of this challenging population. Adherence rates were acceptable in all three studied periods (inpatient, outpatient up to day 100, day 100 up to day 180), ranging from 66 to 77% (89 to 199 min/ week). Most important determinants for adherence were fatigue (p=.004), physical performance (p=.003) and prior exercise engagement (p=.010). The models could explain 16%, 21%, and 55% of variance respectively. However, we also faced some problems that may negatively affect further study results. Exercise contamination of the control group was evident in 54% (89% were walking on a regular basis). Determinants for exercise contamination were higher muscle strength (p=.025) and less fatigue (p=.050). Total variance explained was 29%. The results give important implications for future exercise trials and data analysis.

6.2 Discussion

So far, the PETRA study is the largest randomized controlled exercise intervention trial in HCT patients. RCTs are known as gold-standard in evaluating interventions. The study encompasses two distinct periods of the previously introduced PEACE cancer control framework: during and after treatment; in some cases an additional palliative care or resumption period is included. This provides a unique opportunity to examine effects of exercise throughout the whole transplantation, and rehabilitation process. Other larger studies in this field used mixed populations of allogeneic and autologous transplanted patients and applied the intervention either during or after hospital stay (1, 2). Due to the different nature and biology of allogeneic and autologous transplantation process (autologous HCT requires

no immune suppression and has no risk of GvHD since the transplanted cells originate from the patient itself), the recovery process after HCT may be quite different between both transplanted groups; this complicates the conclusions drawn in previous studies from these heterogeneous populations.

The rationale for the PETRA study was a retrospective analysis of survival data of our first RCT, where a possible effect of exercise on overall survival could be shown (3). Additionally to the first RCT (4), the intervention duration in the PETRA study was extended up to one year, and a one year follow-up measurement time point was included. In addition, we stratified our randomisation process on relevant prognostic factors (e.g. remission state), and we included gold-standard physical performance measurements (CPET, isometric and isokinetic muscle strength measurements and accelerometers) to assess more objective fitness parameters in order to enhance internal validity. The additional use of these assessment procedures gives us the possibility to compare the common used procedures, e.g. six-minute walk test, with the gold-standard methods. This will give us important information about interpretation of physical performance data in the future. Furthermore, detailed GvHD documentation and blood samples at each measurement time point were included to study more mechanistic questions (see chapter 3).

A first analysis of the PETRA data revealed a representative sample which allows generalisation of outcomes. 73% of eligible patients could be included in the trial, a relatively high number compared with other studies. For example, Knols et al. included only 41% in their supervised intervention after HCT (2), Shelton et al. included 24% (5) and Courneya et al. included only 26% of eligible lymphoma patients (9% of all screened patients) in their HELP-trial (6). The dilemma of recruiting only highly motivated patients and patients in good health status, who are more likely to adhere to a given exercise prescription, versus a representative sample, including also patients with more co-morbidities and side-effects, was discussed in chapter 5. Thus, patients who do not like exercise or do not feel that they can master the program may refuse participation right from the beginning and limit attrition.

A recent review described the retention and adherence in exercise studies in the transplant setting. From 20 included studies, mean sample size was 49.9 (SD 39.38), providing samples of 10 to 135 patients. The retention was surprisingly high (82%) and 24% of drop-out reasons were attributed to recurrent disease (7). However, particularly in small studies, the retention was up to 100%, indicating a very selective sample. In the PETRA study, recurrence was no reason for drop-out or not performing our testing procedures (data not shown). Depending on the type of disease recurrence and the following therapy, patients were able (after adaption) to continue our exercise program. However, due to the small number of recurrent disease during the first 180 days we did not perform any statistical analysis, for example, to examine the effect of recurrence on adherence.

The inclusion of a selective sample results in an emphasis on internal validity. On the other hand, however, it limits external validity of findings (generalisability) and may confound

translation of evidence based exercise programs into clinical practice. Courneya et al. determined adherence as one of the key differences between efficacy (high adherence) and effectiveness (real world conditions, lower adherence) trials (8). Therefore, our adherence data must be seen in the light of the underlying population and the degree of supervision, since supervised exercise interventions may have higher adherence (9). Unfortunately, the study by Shelton et al. did not report adherence rates in the compared supervised and unsupervised exercise groups and therefore this study gives no further insight into possible effects of supervision in allo-HCT patients (5). In the PETRA study, adherence was acceptable with 66% during allo-HCT, 65% and 77% after allo-HCT, but lower than in comparable studies. Exercise duration increased from 89 minutes per week to 199 minutes per week. In our first RCT we reached adherence rates between 83% and 91% (4), and another study, examining effects of a supervised multimodal exercise intervention in allo-HCT during hospital stay, reported adherence ranging from 80 to 97% (10). Both studies had shorter total intervention duration, known to enhance adherence. Furthermore, when comparing PETRA adherence data to our first RCT, it might be that in the first study selection bias was present, since we included a smaller proportion of patients transplanted in the two centers. In comparison to the length of intervention investigated within the PETRA study (6 months), a pilot study in 24 multiple myeloma patients receiving autologous HCT which investigated an unsupervised home-based exercise program achieved an adherence of 75% (11). Another 8-week feasibility study in deconditioned cancer survivors after chemotherapy reported comparable adherence to a supervised aerobic exercise of 78% (12).

However, due to a lacking standard in reporting adherence data, it is still difficult to compare these data. The most recent review by Kampshoff et al. dealt with adherence and its determinants and summarized the large variety of different measures applied to describe adherence. Studies used for example percentage of the prescribed number of sessions attended, number of completed exercise sessions, average minutes of exercise per week, or meeting exercise goals (13). Furthermore, the CONSORT Statement, used as a worldwide standard to report RCTs, does not require that authors report information about adherence to the tested intervention (14). Therefore, reporting and interpreting adherence data remains insufficient. In our analysis (chapter 5) we reported adherence referring to the previous introduced FITT criteria. We described the number of exercise days/sessions per week and exercise duration (minutes per week). We distinguished between endurance and resistance exercise sessions and could discriminate between different periods during and after treatment. Additionally, we described how many patients were able to exercise more often than the prescribed minimum of three exercise days per week, and how many patients could meet the recommended exercise duration of 150 min exercise per week (15). This detailed adherence description is important for a better comparison between studies and reproducibility. Moreover, it is crucial to allow conclusions about the efficacy of intervention program, and if a given exercise program might be successful when translated into standard care. However, a limitation is that we were not able to give clear adherence to exercise intensity performed, since the main intervention mode was a self-directed home-based training. Patients received

the clear advice which intensity they should target using the BORG RPE-scale (16), and the intensity prescription was re-evaluated during the regular phone calls, but we do not have a consistent documentation of intensity performed.

We also examined possible determinants for adherence in different treatment periods (PEACE framework). To our knowledge, this was the first analysis performed in the HCT setting (chapter 5). Our results were comparable to other studies in different cancer populations that found fatigue, physical performance and exercise history as significant predictors for adherence (13, 17-19). However, all previous studies examined predictors of adherence in one distinct setting, whereas our study looked at determinants in different treatment phases (during and after allo-HCT) and different delivery modes (supervised and home-based). In the first period, our regression model explained 16% of variance of exercise duration, suggesting that during intense treatment and supervision there are other more important factors than those examined. Potential factors may be, for instance, dose of the conditioning chemotherapy prior allo-HCT, previous treatment modalities or co-morbidities. We will consider these factors in further analyses. Explained variance of adherence was 21% after discharge up to day 100. Our results proposed that a good physical performance at discharge heavily contributes to a better adherence to the self-directed exercise program at home. This finding indicates even more that exercise interventions during HCT or even prior HCT are important. Our study could confirm the results of other studies that patients with exercise experience prior treatment had higher adherence (13). Explained variance in this period was 55%. A further new result was that having GvHD (greater than grade 1) did not influence the adherence, indicating that patients suffering from this complication are able to exercise. This is an important finding since there is only one retrospective study that describes the adherence of patients suffering from GvHD to a four-week exercise-based rehabilitation program. In this study only 54% of all 59 patients could complete 80% of the prescribed sessions (20). Furthermore, another review about determinants of adherence focused only on motivational and behavioral factors and concluded that the found predictors e.g. exercise stage of change derived from the transtheoretical model of behavior change, were weak predictors (21).

Providing information on determinants is important information to improve future study designs and to translate programs into clinical care. Our results indicated that special attention to patients with high fatigue levels and low endurance performance is needed to enhance adherence in these subgroups. The recent review by Kampshoff et al. identified all examined determinants of adherence (the 12 included studies investigated associations with 71 determinants!), but only for exercise history moderate evidence could be found. The authors pointed out that methodological issues of the included studies, e.g. small sample size and selection bias, might have resulted in insignificant findings in the performed studies (13). Moreover, the insufficient description of adherence of previous studies makes it impossible at this research state to investigate determinants of adherence regarding type, frequency, intensity and delivery mode (e.g. supervised, home-based) across available studies.

Beside adherence, we further investigated a far less acknowledged problem of exercise intervention trials, a possible contamination of the control group. As described in chapter 5, contamination refers to an exercise engagement in the control group. Only few studies elucidated this possible behavior, although it is known to cause a delusion of the treatment effect which may make it impossible to show any positive results based on an intention-to-treat principle (22, 23). The recent review about exercise oncology research from Jones & Alfano elaborated current research gaps and constituted the consideration of exercise contamination in the control group as an issue that needs to be considered in future trials (24). We assessed contamination via questionnaire at day 180 after allo-HCT. As presented in chapter 5, 89.6% of control group participants stated that they were walking on a regular basis (mean duration 4 hours per week), and 54.2% listed that they were doing some kind of sportive activity. When comparing these data to our intervention group, the most frequent exercise performed at this time point was endurance exercise (mainly performed as walking). Given the long duration of weekly walking activity stated by the control group, we think that the exercise dose received was quite similar in both groups in terms of endurance exercise duration. This information will give us additional information when analyzing the primary and secondary outcome parameters of the PETRA study (see chapter 3), and may help to explain possible low intervention effects.

However, assessment methods of both, adherence and contamination rely on self-report, and for contamination a recall bias may be affecting the results since the patients needed to describe activities retrospectively (25, 26). Therefore, our objectively assessed physical activity data obtained with accelerometers at each measurement time point will give important information not only on walking duration, but also on achieved intensity (metabolic equivalent, METs). However, one need to consider that resistance training activities cannot be determined using accelerometers. In our first RCT, physical activity was measured with pedometers. Interestingly, prior to and after transplantation the control group reached non-significantly more steps than the exercise group (4). Courneya et al. described that participants of the exercise group might compensate for the exercise sessions by reducing other forms of physical activity in daily living (17).

In the PETRA study, significant determinants for exercise contamination were high isometric muscle strength and low physical fatigue levels; total variance that could be explained was 29.4% (see chapter 5). This result supports our findings regarding determinants for adherence, since a physical performance measurement and fatigue also strongly influence adherence. These consistent results underline the importance to consider these aspects when prescribing exercise programs in allo-HCT patients. Possible reasons for the high contamination rate were discussed in chapter 5, and the question arises if there are any solutions that can help to overcome this problem. In the literature some ideas for control-group designs were discussed. For example, wait-list groups, attention-control groups or including a non-exercise intervention (24). In the PETRA study a non-exercise control group (progressive muscle relaxation) was selected, given the long intervention period. When communicating with the

participants, we always point out that our relaxation program is an intervention too in that we are interested in. We therefore hope that patients in the control group do not feel disadvantaged and consequently may start to exercise by themselves.

A more methodological limitation is that we did not use our physical performance data assessed with gold-standard assessment procedures (CPET and isometric/ isokinetic muscle strength measurement) for the regression models of adherence and contamination as these assessment procedures were not performed at two included measurement time points (discharge and day 100). Therefore, we decided to use the data from the 6-minute-walk test and hand-held dynamometer instead, so that we could include all time-points in our analysis. These assessments procedures have proven to be reliable and are frequently used in this population (27-30).

Current research questions in the field of exercise in cancer patients/ survivors include the need for more personalized exercise prescriptions, and information on dose-response relationships. The review by Buffart et al. summarized the currently available exercise guidelines for cancer survivors and concluded that these guidelines were rather generic and more information was needed to improve these recommendations (31). Thus, it is recommended to use exercise prescriptions developed for healthy adults, as described in chapter 4. To our knowledge, we were the first group, who compared these exercise prescriptions in terms of endurance training intensity with data driven from a cancer population. Our analyses revealed that given intensities may not meet targeted intensity classes prior to and 180 days after allo-HCT, therefore when using the current guidelines exercise intensity may be over- or underestimated. This is not only a problem when prescribing endurance exercise, but also when comparing previous training studies, because the targeted intensity in the different studies might have been quite different. As constituted in chapter 4, it is of great relevance to improve exercise prescription in cancer patients, but our data show as well that there is a large variation in observed values representing the different intensity classes. We therefore suggest, that optimal individually tailored exercise prescription can only be determined from an objective evaluation of the individual's acute response to exercise (CPET), general intensity recommendations remain universal in nature and should not be used in studies. To improve exercise prescription in hematological cancer patients, we provided a table, similar to the table from ACSM, with exercise intensities derived from allo-HCT patients (see chapter 4). This table can be used to define, for example, moderate or vigorous intensity. Furthermore, by using the tables, exercise intensities applied in different studies can be compared, even when studies used different parameters for intensity prescription (e.g. %HRR or $\%P_{max}$). Some previous studies in the HCT setting relied on equations (e.g. *220-age*) to determine training intensity (2, 10, 32). However, our results show that this approach results in very imprecise values too and should not be recommended. It needs to be noted that our exercise test protocol was not ideal for patients with less physical capacity because of a relatively high first stage (50 watts, see discussion chapter 4). Just recently, a German working group developed a proposal to harmonize assessment procedures

in the oncological setting. Within these recommendations a more appropriate CPET protocol is proposed which will be used for future studies (33). Moreover, our findings regarding the different intensities showed up to be consistent in other cancer populations. Our group performed the same analysis in a population with 52 breast cancer patients after chemotherapy and could demonstrate that the ACSM classification in this population is only valid when $\%HR_{max}$ is used. Using %HRR resulted in a considerably too high exercise intensity, and using $\%VO_{2max}$ in too low intensities (results not part of this thesis) (34). Defining precise intensity classes is key when more sophisticated questions are to be addressed, for example dose-response modulations.

First RCTs were conducted to examine dose-response modulations in cancer populations. In the CARE-Trial, an RCT including 301 breast cancer patients during chemotherapy, a standard dose exercise program (25-30 min aerobic exercise 2 times per week) was compared to a higher dose (50-60 min per week) and a combined intervention (50-60 min aerobic and resistance exercise per week). The higher exercise dose was associated with better PROs, for example pain and other physical aspects, in breast cancer patients during chemotherapy; however, there were no differences between groups for the primary endpoint physical functioning (35). Though, in this study the exercise intensity, determined at percentages from VO_{2max}, was the same in all groups. The exercise dose was different only in terms of exercise duration and type of exercise performed. Nevertheless, the prescribed intensity classes in the CARE-Trial correspond to our findings of exercise intensities in breast cancer patients (34, 35). However, in a study with healthy sedentary adults, for example, a more appropriate design was used: Different exercise intensities (moderate vs. high intensity) were determined by 45-55% of HRR for moderate, and 65-75% HRR for high intensity (36). However, next generation studies are on the way comparing the effects of different endurance exercise intensities in cancer patients. For example, Jones et al. are conducting an RCT in 174 postmenopausal women following primary therapy and comparing supervised moderate-intensity aerobic training (150 min/ week 60-70% VO_{2peak}) to supervised high-intensity training (150 min/week 60 – 100% VO_{2peak}) for 18 weeks. A third group performs stretching exercise for comparison. The primary outcome is VO_{2peak} (37).

The different available guidelines for exercise prescription in cancer patients recommend to individually tailor exercise programs to the needs and current health status of the patients. An interesting study further underlines the need for more research in this area. The researchers examined if the current guidelines such as the ACSM guidelines for cancer survivors could be used to prescribe unsupervised exercise in 251 non-metastatic colon cancer survivors six months after completing curative treatment. They found out that it was only possible in 21% of survivors (or 42% when excluding survivors with common co-morbidities e.g. diabetes and hypertension). The authors concluded that guidelines for cancer survivors might also require other services such as supervision and staff with knowledge to appropriately tailor exercise. Furthermore, they pointed out that more research on safety, contraindications and adverse events (risk and harms) would enhance the likelihood of physicians to prescribe or

recommend exercise (38). However, this study was a retrospective study, and no information is available if the survivors were able to follow the guidelines. This examination points out that more studies are needed to enhance exercise prescriptions and that information on how to individualize exercise programs is lacking. Moreover, it is not clear which factors are important to consider when prescribing exercise in cancer patients and which factors may explain exercise response in cancer patients. Hereby, baseline physical fitness might be an essential aspect.

In the non-cancer population, long established evidence from large cohort studies shows that low fitness is an independent predictor of mortality in men and women. Additionally, fit subjects with further known risk factors like smoking, elevated blood pressure, elevated cholesterol level had lower adjusted death rates than subjects with low fitness (39). For example, in a prospective cohort study in 9,777 men the gain in fitness parameters was associated with a 44% reduction in mortality risk (40), and an improvement of 3.5ml/kg/min maximum oxygen uptake has been found to improvement in survival by 12% (41). Furthermore, there is indisputable evidence that regular physical activity contributes to the prevention of several chronic diseases, e.g. cardiovascular diseases (42). In cancer patients first evidence suggests that the physical performance seems to have an important influence on clinical outcomes, such as survival. For example in patients with metastatic non-small cell lung cancer functional capacity, measured via 6-minute-walk test or CPET, was an independent predictor of survival. It contributed to an improved risk stratification and was therefore suggested to complement traditional prognostic markers (43, 44). Additionally, a cohort study in 32 patients prior allogeneic or autologous HCT showed a higher risk of mortality in patients who had less than 16ml/kg/min VO_2 uptake (45), and the survival data of our first RCT also suggest that physical fitness is a protective factor against all-cause mortality and non-relapse mortality (3).

To our knowledge, no study so far investigated a possible different response to exercise in cancer patient groups with different fitness levels. This information would help to understand the mechanisms of exercise in cancer patients during treatment. Since fitness plays such an important role regarding mortality in non-cancer subjects, and first evidence underlines similar effects also for some cancer populations, we performed a retrospective analysis of the experimental group of the first RCT (4), investigating the different training responses of different patients classified as *fit* (chapter 2). Results show that the individual response between *fit* and *unfit* groups was significantly different, with more benefit for initial *unfit* patients. Therefore, the results support the general recommendation to individually tailor the exercise prescription. Furthermore, the results show that even patients with low physical performance can safely exercise throughout the intensive treatment period of allo-HCT. This finding is of utmost importance, since exercise is often not recommended in these patients, and first studies in cancer patients and allo-HCT patients show a possible association of physical fitness prior allo-HCT and survival (see above). The methodological drawback of a retrospective analysis was discussed in chapter 2. Some questions, however, remain to be

answered. It seems that in *unfit* patients the intensity of exercise prescription was appropriate, whereas in *fit* patients the dose of exercise might have been not high enough to obtain positive effects on the physical level. Interestingly, the adherence of both groups was similar, bearing in mind, that adherence was measured in sessions per week. Unfortunately, we cannot give further details on exercise duration or exercise intensity achieved. Intensity was determined by the patients using the BORG RPE scale (16), however, we do not know if targeted exercise intensity was reached. Therefore, it might be that *fitter* patients exercised at an individually lower intensity level, not reaching the optimal training load to achieve optimal effects. When we compared the *fit* exercise group to the control group, there was no significant difference, but a positive trend in favor of the exercise group. Nevertheless, it needs to be noted that the groups for these comparisons were quite small, influencing the non-significant finding. When looking at the graphical distribution of both groups (see chapter 2, figure 3), the exercising *fit* patients were superior to the control group patients.

A review in non-cancer populations addressed the question of inter-individual variation in exercise response to regular exercise training and showed that subjects can have individual differences in responsiveness. Age, sex and ethnic origin were no major determinants of responsiveness, whereas pre-training level had considerable impact in some cases (46). In the HERITAGE family study where healthy individuals exercised at the same level of %VO_{2max} intensity, it was suggested that the variation in training response may be partly explained by genetic components (47). Furthermore, the DREW study included 464 healthy post-menopausal women to examine predictors of exercise non-response (measured VO_{2max}) after 6 months of training (intensity 50% VO_{2max}). Despite high adherence (~92%) there was a large amount of variability. Predictor of VO_{2max} non-response was (among others) baseline VO_{2max} value. Thus, women who were initially less fit had greater changes of improving their VO_{2max} (48). However, this result was not surprisingly, since 50% VO_{2max} intensity is relatively low, and as described earlier, in more *fitter* subjects the exercise intensity needs to be more intense.

In the previously mentioned CARE-Trail in breast cancer patients, moderators of exercise response were analyzed too, and fitter patients were more likely to benefit from higher-dose exercise, whereas less fit patients showed no benefits of higher dose exercise. Moreover, in accordance with our results, no interaction effect of fatigue and patient reported physical function could be observed in this study (49). These results support our finding that the exercise dose needs to be individually determined dependent on the baseline fitness in order to obtain an optimal effect for an individual patient. Furthermore, regarding a more methodological consideration, baseline fitness should be considered as a stratification variable in future studies. A meta-analysis examined the dose-response relationship regarding psychological outcomes, e.g. fatigue and quality of life, in breast cancer patients. The authors found that studies that applied a lower dose moderate exercise (<12MET h/week, ~90-120 min) were more efficacious in reducing fatigue than studies that investigated higher exercise doses. However, to improve quality of life outcomes, studies with higher dose exercise (>20

MET h/week) were more efficient (50). Interestingly, we could not find an association between baseline fitness mediated exercise response and PROs in our study (chapter 2). With respect to quality of life outcomes during treatment, the actual Cochrane review also suggests that more intense exercise interventions (moderate/ vigorous intensity versus mild-intensity) were also more effective (51). These results emphasize the need for future dose-response studies.

6.3 Conclusion and clinical implications

The ultimate goal should be that exercise is prescribed as a routine part in hematological cancer patients or generally in cancer treatment. To meet this aim, we need further information about tolerability and positive effects of conducted exercise programs throughout the whole cancer trajectory. To interpret previous results adequately, it is of importance to distinguish between efficacy trials and effectiveness trials, thus, considering the studied population in more detail. The PETRA study achieved a high recruitment rate (73%), indicating a representative sample. Beside a detailed description of the intervention program, detailed adherence data according to the FITT formula enables reproducibility and translation of programs into clinical care. The PETRA study accomplished this target when describing in detail the frequency, duration and the exercise mode performed in different treatment periods during and after treatment. Such detailed description will also be crucial when analyzing more sophisticated questions, e.g. dose-response modulations. Adherence was with 66 to 77% (89 to 199 min/ week) acceptable. Determinants of adherence provide important information on interaction of different physical, social, behavioral and medical factors with exercise participation. This information gives insight knowledge for designing exercise programs, on how to personalize programs and on how to target specific subgroups. Our results suggest a focus on problems regarding fatigue and physical performance when designing exercise programs in order to improve adherence. Furthermore, we think that including more comprehensive treatment data such as previous chemotherapy modalities, type of disease and co-morbidities, would be valuable in this kind of analysis. A closer look on activities performed in the control group revealed a serious problem of exercise contamination in the PETRA study. A large proportion of control group patients were physically active 180 days after transplantation (54% sport activity, 89% regular walking). Further analysis of group comparisons will illustrate to what extend this will have an impact on intention-to-treat analysis. Since contamination received little attention in RCTs, it is not clear how contamination influenced results in previous studies. Therefore, future studies should focus more on a possible contamination effect, and new strategies for control group designs are needed.

Even though exercise guidelines for cancer patients exist, these recommendations remain rather general and adopt exercise guidelines developed for healthy subjects. A comparison of intensity classes for endurance training prescription revealed that the commonly used

guidelines are not valid in hematological cancer patients (prior to and 180 days after allo-HCT) and would result in over- or underestimation of exercise intensity. The tables created can be used not only for exercise prescription, but also for comparison of different exercise intensities performed in other studies. Furthermore, these tables provide a basis for dose-response studies. The analysis of the different exercise responses in patients with different initial fitness levels revealed that patients who were physically de-conditioned prior transplantation benefited more from exercise during and after allo-HCT. This result is of high clinical importance, since evidence of a possible association between initial fitness and survival after allo-HCT exists. Moreover, these data show that exercise is feasible even in de-conditioned patients and suggest focusing more on this patient group. Moreover, the data underline the importance to individually tailor exercise prescription depended on current fitness status, and the need to identify individuals who may benefit in particular or who need special attention.

6.4 Future Directions

Results of previous research and results of this thesis underline the great potential of exercise in hematological cancer patients. However, further important research areas need to be considered in future trials.

Pre-Training
Given the low physical performance of allo-HCT patients already prior transplantation and the possible association with higher post-transplant mortality in initially unfit patients, the time point prior HCT seems to be an important research area. It appears to be essential to start an individualized exercise program as early as possible. This concept already proves feasibility in lung cancer patients, where exercise was implemented during waiting time for surgical resection (52). The results of this thesis support this idea of pre-training with the following aspects: we proved that *unfit* patients can exercise safely and are more likely to benefit from exercise (gain during treatment) than more *fitter* patients. The results also show that physical fitness seems to be an important determinant for adherence and contamination after allo-HCT, therefore an enhancement of physical activity in this period may be important. We could also demonstrate in our first study that an exercise program prior transplantation is feasible (4). This pre-training approach would complement the traditional rehabilitation procedure and implement an additional preparation period. This would ensure a comprehensive care throughout the whole PEACE framework. However, implementing exercise prior allo-HCT will be even more challenging because time from decision for allo-HCT to transplantation is short and patients are often still under treatment. On the other hand, the preparation for transplantation is associated with many clinical examinations, providing a possibility to get in close and frequent contact with the patients.

Exercise Delivery

Given the high frequency of hospital visits prior to and after allo-HCT, integration of exercise programs into standard hospital care seems to be practicable. One idea would be to extend our home-based exercise program during outpatient periods to a partly supervised program. This would ensure a closer monitoring and better adaption of exercise dose to clinical status. Additionally, more focus on exercise intensity could be given. This is an important consideration since the results of this thesis suggest that in *fitter* patients the training load of the mainly home-based self-directed exercise program might not have been high enough to obtain the same positive effects as in the *unfit* patients. In addition, more mechanistic questions regarding dose-response effects could be studied. Additionally, in this thesis, endurance exercise intensity classes for hematological cancer patients were defined. These intensity classes could be applied and further tested in supervised sessions. Interestingly, a recent RCT in 61 lung cancer patients after surgery proved the feasibility of a high intensity exercise program (80-95% HR_{max}) in combination with resistance exercises. Positive results were seen for different outcomes, including VO_{2max}, muscle strength, muscle mass and quality of life (53). One small pilot study examined an outpatient exercise program during treatment for acute leukemia, but the program only comprised supervised sessions. However, the adherence was with 73% relatively high, suggesting that this kind of intervention will be feasible (54). An RCT in 70 patients is currently ongoing to prove these pilot findings in a 12-week intervention (55).

Improving Adherence

The adherence rates of the PETRA study show, that home-based programs over a longer duration are feasible and acceptable. Further analysis of the data will show how effective the program is on a physical and psychosocial level. The experience with the first included 153 patients illustrates that a highly flexible exercise program is necessary. The exercise program needs to be performed outpatient at home as well as inpatient in the patient room, when patients are readmitted to hospital. In our study we ensured supervised exercise sessions in such cases, also when patients were on a different ward. In some circumstances, we could use an exercise room from the physiotherapy department (with resistance training machines and cycle ergometers), which was very well accepted by the patients. Therefore, incorporating further supervised exercise sessions during outpatient visits might be a promising adjunct that will help to build a bridge between home-based activities and hospital-based supervised exercise training. Another idea to improve adherence and to make interventions more interesting for the individual patient is to provide a referral to an exercise facility close to the patient's home. This approach was partly tested in the PETRA study using the *OnkoActiv Network*, developed by the working group Physical Activity, Exercise and Cancer at the NCT. Furthermore, an internet-based training platform could be another tool to expand the training possibilities. Within the PETRA study such a platform was developed. Using this platform, an adaptive exercise program, feedback on training progress and the possibility to contact a study therapist is provided online. This platform was pilot-tested within the PETRA study as well, and proved good acceptability (56).

Taken into account the individual preferences, physical conditions, exercise history and travel issues a broad concept is needed, including different exercise opportunities. Only this ensures to match the needs and preferences of the individual patient to an optimal individualized exercise program and will result in appropriate adherence. Furthermore, variation and adoption of exercise prescription and regular communication to physician/ oncologist must be standard practice to ensure safety and a successful exercise program. Interestingly, a large multicenter prospective study in 711 patients before allogeneic or autologous transplantation concluded that brief exercise counselling prior transplantation had no effect on physical activity after transplantation or other outcomes such as quality of life (57). These data underline that there is a high need for exercise programs, guided by exercise experts and as part of clinical care, in particular for such a challenging population.

Basic research

Beside more research on health science and the integration of programs in clinical praxis (effectiveness trials), more mechanistic questions need to be studied. A recent publication of our group described the current level of evidence regarding possible physiologic and molecular mechanisms of exercise as preliminary (58). Within the PETRA study blood samples are drawn (and stored for further analysis) and a detailed documentation of GvHD occurrence, localization and severity is implemented in a highly standardized manner. This will be a unique opportunity to examine the interaction of exercise/ physical activity and immune markers, known to cause inflammation and GvHD. Previous studies in allo-HCT either did not include the treatment period in which chronic GvHD plays a role, or excluded patients with GvHD. Therefore, information on a possible interaction of exercise with chronic GvHD is unknown. Interestingly, first experimental studies in mouse-models established the hypothesis that exercise might influence the severity of chronic GvHD and survival positively by modulating an immune response (IL-4, TNF-α, CD4 lymphocytes) (59, 60). However, the sample was very small and the results have to be interpreted with caution. Yet, data in humans are not available. When looking deeper into this possible relationship, it will be of great importance to have detailed adherence data to consider a possible dose-response relationship. This will be important because there might be a possible non-linear relationship, indicating that a very high exercise dose might have negative effect on GvHD (61). Another interesting and less studied topic is to gain more insight into possible mechanisms on biomarker level regarding cancer-related fatigue. Recently, this topic was considered as high-priority research area (62). Here, the PETRA study will have great opportunities to study the interaction between inflammation and fatigue in a longitudinal pattern within an exercise intervention trial.

Effects of Exercise on Side-Effects of Cancer Treatment

Novel, innovative treatment regimens, such as immunomodulatory drugs (e.g. thalidomide, lenalidomid, bortezomib) and traditional chemotherapeutic agents, such as vincristine, cisplatin and methotrexat have led to improved outcomes in hematologic cancer patients, but are frequently associated with a dose-limiting peripheral neuropathy (CPIN) (63-65). CPIN is

caused by a structural and functional damage to nerve fibers. A first RCT in lymphoma patients could show promising results of sensorimotor training on quality of life and CPIN symptoms (66). Since CPIN is a side-effect not only affecting particular cancer entities, but affecting also groups of patients who receive certain treatment regimens, it may be more appropriate to study the effect of exercise on these patient groups with high risk of CPIN, independent of the type of cancer. A first consideration in this direction was done by Wiskemann & Scharhag-Rosenberger from our group. They introduced the side-effect-oriented therapy pathway concept as a model to prescribe exercise on the basis of current evidence (67). Particularly in hematological cancer patients it seems valuable to further translate this approach into research, since a lot of different cancer entities exist and sometimes patient groups are quite small. In our two studies this approach was partly adopted when including patients with different entities (e.g. leukemia, lymphoma), but following the same treatment concept (allo-HCT), resulting in the same side-effects (e.g. GvHD).

To pursue this idea further, beside CPIN, another research area that will be important in hematological cancer patients in the future is the effect of exercise on cardiotoxicity. Many chemotherapeutic agents, known to cause damage in the heart muscle, are frequently used in hematological cancers (e.g. doxorubicin, daunorubicin, cyclophospamide, idarubicin, and clofarabin). Antracyclines containing chemotherapy regimens are associated in a dose-dependent mode with left ventricular dysfunction (68). In these settings, aerobic exercise might be a powerful tool because it may improve systolic and diastolic function as well as general exercise tolerance (69). Whereas most studies investigated protective effects of exercise on cardiac damage in animal models (mice and rat studies) (70), there is only one study in humans that investigated cardiac function following exercise intervention during chemotherapy treatment for breast cancer, but with inconclusive results (71). Also molecular targeted therapeutics can have cardiotoxic effects which may be prevented by aerobic exercise (72).

Exercise in High-Risk Groups

Implementing exercise interventions in multiple myeloma patients is an additional challenge due to an extensive bone destruction process associated with a high fracture risk (73). We faced this problem when including multiple myeloma patients in the PETRA study. Furthermore, a frequent side-effect of different treatment regimens used is osteoporosis (74, 75). Therefore, more information is needed regarding not only on the stability of bone structure when performing exercise, but also on a possible interaction of bone destruction processes and exercise (resistance training). A first RCT in 106 postmenopausal non-metastatic and non-osteoporotic breast cancer patients could demonstrate that a one-year resistance and impact (jump) exercise could prevent bone loss of the lumbar spine (76). Moreover, an RCT examined the feasibility of resistance training (isometric) in 60 patients with bone metastases (without fracture risk) under radiation therapy. Results were promising, indicating less pain and better physical function. Interestingly, no progression of metastases was seen in the experimental group after 3 months, whereas progression was evident in 17%

of control group patients (77). In the PETRA study we included 18 patients with multiple myeloma so far and a subgroup analysis will be performed in the future to examine if our mixed intervention program will have had any benefit regarding characteristic side-effects, for instance pain.

In conclusion, this thesis established a basis for further research questions, including ideas for future studies, enhanced targeted exercise delivery, innovative research questions regarding effects of exercise on cancer treatment complications and basic scientific approaches to understand mechanisms. In the view of the vast potential of exercise in this broad scope of applications it becomes increasingly important to build up multidisciplinary research teams and integrate exercise science into clinical patient care. Starting from this thesis, a new study is being planned, investigating a pre-training approach in allo HCT patients.

6.5 References

1. Baumann FT, Zopf EM, Nykamp E, Kraut L, Schule K, Elter T, Fauser AA, and Bloch W. 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.
2. Knols RH, de Bruin ED, Uebelhart D, Aufdemkampe G, Schanz U, Stenner-Liewen F, Hitz F, Taverna C, and Aaronson NK. 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.
3. Wiskemann J, Kleindienst N, Kuehl R, Dreger P, Schwerdtfeger R, and Bohus M. Effects of physical exercise on survival after allogeneic stem cell transplantation. *International Journal of Cancer*. 2015.
4. Wiskemann J, Dreger P, Schwerdtfeger R, Bondong A, Huber G, Kleindienst N, Ulrich CM, and Bohus M. Effects of a partly self-administered exercise program before, during, and after allogeneic stem cell transplantation. *Blood*. 2011;117(9):2604-13.
5. Shelton ML, Lee JQ, Morris GS, Massey PR, Kendall DG, Munsell MF, Anderson KO, Simmonds MJ, and Giralt SA. A randomized control trial of a supervised versus a self-directed exercise program for allogeneic stem cell transplant patients. *Psychooncology*. 2008;18(4):353-9.
6. Courneya KS, Sellar CM, Stevinson C, McNeely ML, Peddle CJ, Friedenreich CM, Tankel K, Basi S, Chua N, Mazurek A, and Reiman T. Randomized controlled trial of the effects of aerobic exercise on physical functioning and quality of life in lymphoma patients. *J Clin Oncol*. 2009;27(27):4605-12.
7. Hacker ED, and Mjukian M. Review of attrition and adherence in exercise studies following hematopoietic stem cell transplantation. *Eur J Oncol Nurs*. 2014;18(2):175-82.
8. Courneya KS. Efficacy, effectiveness, and behavior change trials in exercise research. *Int J Behav Nutr Phys Act*. 2010;7:81.
9. Velthuis MJ, Agasi-Idenburg SC, Aufdemkampe G, and Wittink HM. The effect of physical exercise on cancer-related fatigue during cancer treatment: a meta-analysis of randomised controlled trials. *Clin Oncol (R Coll Radiol)*. 2010;22(3):208-21.
10. Jarden M, Baadsgaard MT, Hovgaard DJ, Boesen E, and 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.
11. Coleman EA, Coon S, Hall-Barrow J, Richards K, Gaylor D, and Stewart B. Feasibility of exercise during treatment for multiple myeloma. *Cancer Nurs*. 2003;26(5):410-9.
12. Broderick JM, Guinan E, Kennedy MJ, Hollywood D, Courneya KS, Culos-Reed SN, Bennett K, DM OD, and Hussey J. Feasibility and efficacy of a supervised exercise intervention in de-conditioned cancer survivors during the early survivorship phase: the PEACH trial. *J Cancer Surviv*. 2013;7(4):551-62.
13. Kampshoff CS, Jansen F, van Mechelen W, May AM, Brug J, Chinapaw MJ, and Buffart LM. Determinants of exercise adherence and maintenance among cancer survivors: a systematic review. *Int J Behav Nutr Phys Act*. 2014;11(1):80.
14. Schulz KF, Altman DG, Moher D, and Group C. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. *BMC Med*. 2010;8:18.
15. Schmitz KH, Courneya KS, Matthews C, Demark-Wahnefried W, Galvao DA, Pinto BM, Irwin ML, Wolin KY, Segal RJ, Lucia A, Schneider CM, von Gruenigen VE, and Schwartz AL. American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. *Med Sci Sports Exerc*. 2010;42(7):1409-26.
16. Garber CE, Blissmer B, Deschenes MR, Franklin BA, Lamonte MJ, Lee IM, Nieman DC, Swain DP, and American College of Sports M. 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.

17. Courneya KS, Segal RJ, Reid RD, Jones LW, Malone SC, Venner PM, Parliament MB, Scott CG, Quinney HA, and Wells GA. Three independent factors predicted adherence in a randomized controlled trial of resistance exercise training among prostate cancer survivors. *J Clin Epidemiol*. 2004;57(6):571-9.
18. Courneya KS, Stevinson C, McNeely ML, Sellar CM, Peddle CJ, Friedenreich CM, Mazurek A, Chua N, Tankel K, Basi S, and Reiman T. Predictors of adherence to supervised exercise in lymphoma patients participating in a randomized controlled trial. *Ann Behav Med*. 2010;40(1):30-9.
19. Shang J, Wenzel J, Krumm S, Griffith K, and Stewart K. Who will drop out and who will drop in, exercise adherence in a randomized clinical trial among patients receiving active cancer treatment. *Cancer Nurs*. 2012;35(4):312-22.
20. Morris GS, Brueilly KE, Scheetz JS, and 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.
21. Husebo AM, Dyrstad SM, Soreide JA, and Bru E. Predicting exercise adherence in cancer patients and survivors: a systematic review and meta-analysis of motivational and behavioural factors. *J Clin Nurs*. 2013;22(1-2):4-21.
22. Mock V, Pickett M, Ropka ME, Muscari Lin E, Stewart KJ, Rhodes VA, McDaniel R, Grimm PM, Krumm S, and McCorkle R. Fatigue and quality of life outcomes of exercise during cancer treatment. *Cancer Pract*. 2001;9(3):119-27.
23. Courneya KS, Friedenreich CM, Quinney HA, Fields AL, Jones LW, and Fairey AS. A randomized trial of exercise and quality of life in colorectal cancer survivors. *Eur J Cancer Care (Engl)*. 2003;12(4):347-57.
24. Jones LW, and Alfano CM. Exercise-oncology research: past, present, and future. *Acta Oncol*. 2013;52(2):195-215.
25. Trost SG, and O'Neil M. Clinical use of objective measures of physical activity. *Br J Sports Med*. 2014;48(3):178-81.
26. Ainsworth BE, Caspersen CJ, Matthews CE, Masse LC, Baranowski T, and Zhu W. Recommendations to improve the accuracy of estimates of physical activity derived from self report. *J Phys Act Health*. 2012;9 Suppl 1:S76-84.
27. Knols RH, Aufdemkampe G, de Bruin ED, Uebelhart D, and Aaronson NK. Hand-held dynamometry in patients with haematological malignancies: measurement error in the clinical assessment of knee extension strength. *BMC Musculoskelet Disord*. 2009;10:31.
28. Rostagno C, and Gensini GF. Six minute walk test: a simple and useful test to evaluate functional capacity in patients with heart failure. *Intern Emerg Med*. 2008;3(3):205-12.
29. Schmidt K, Vogt L, Thiel C, Jager E, and Banzer W. Validity of the six-minute walk test in cancer patients. *Int J Sports Med*. 2013;34(7):631-6.
30. Stark T, Walker B, Phillips JK, Fejer R, and Beck R. Hand-held dynamometry correlation with the gold standard isokinetic dynamometry: a systematic review. *PM R*. 2011;3(5):472-9.
31. Buffart LM, Galvao DA, Brug J, Chinapaw MJ, and Newton RU. Evidence-based physical activity guidelines for cancer survivors: current guidelines, knowledge gaps and future research directions. *Cancer Treat Rev*. 2014;40(2):327-40.
32. Mello M, Tanaka C, and Dulley FL. Effects of an exercise program on muscle performance in patients undergoing allogeneic bone marrow transplantation. *Bone Marrow Transplant*. 2003;32(7):723-8.
33. Scharhag-Rosenberger F, Becker T, Streckmann F, Schmidt K, Berling A, Bernardi A, Engeroff T, Exner AK, Gutekunst K, Hofmeister D, Jensen W, Kähnert H, Kneis S, Limbach M, and Steindorf K. Recommendations for Assssemnt Methods for Exercise Trials with Cancer Patients. *Deutsche Zeitschrift für Sportmedizin*. 2014;65:304-13.

34. Scharhag-Rosenberger F, Kuehl R, Klassen O, Schommer K, Schmidt ME, Ulrich CM, Wiskemann J, and Steindorf K. Exercise training intensity prescription in breast cancer survivors: validity of current practice and specific recommendations. *J Cancer Surviv*. 2015.
35. Courneya KS, McKenzie DC, Mackey JR, Gelmon K, Friedenreich CM, Yasui Y, Reid RD, Cook D, Jespersen D, Proulx C, Dolan LB, Forbes CC, Wooding E, Trinh L, and Segal RJ. Effects of exercise dose and type during breast cancer chemotherapy: multicenter randomized trial. *J Natl Cancer Inst*. 2013;105(23):1821-32.
36. Duncan GE, Anton SD, Sydeman SJ, Newton RL, Jr., Corsica JA, Durning PE, Ketterson TU, Martin AD, Limacher MC, and Perri MG. Prescribing exercise at varied levels of intensity and frequency: a randomized trial. *Arch Intern Med*. 2005;165(20):2362-9.
37. Jones LW, Douglas PS, Eves ND, Marcom PK, Kraus WE, Herndon JE, 2nd, Inman BA, Allen JD, and Peppercorn J. Rationale and design of the Exercise Intensity Trial (EXCITE): A randomized trial comparing the effects of moderate versus moderate to high-intensity aerobic training in women with operable breast cancer. *BMC Cancer*. 2010;10:531.
38. Brown JC, and Schmitz KH. The prescription or proscription of exercise in colorectal cancer care. *Med Sci Sports Exerc*. 2014;46(12):2202-9.
39. Blair SN, Kampert JB, Kohl HW, 3rd, Barlow CE, Macera CA, Paffenbarger RS, Jr., and Gibbons LW. Influences of cardiorespiratory fitness and other precursors on cardiovascular disease and all-cause mortality in men and women. *JAMA*. 1996;276(3):205-10.
40. Blair SN, Kohl HW, 3rd, Barlow CE, Paffenbarger RS, Jr., Gibbons LW, and Macera CA. Changes in physical fitness and all-cause mortality. A prospective study of healthy and unhealthy men. *JAMA*. 1995;273(14):1093-8.
41. Myers J, Prakash M, Froelicher V, Do D, Partington S, and Atwood JE. Exercise capacity and mortality among men referred for exercise testing. *N Engl J Med*. 2002;346(11):793-801.
42. Warburton DE, Nicol CW, and Bredin SS. Health benefits of physical activity: the evidence. *CMAJ*. 2006;174(6):801-9.
43. Jones LW, Hornsby WE, Goetzinger A, Forbes LM, Sherrard EL, Quist M, Lane AT, West M, Eves ND, Gradison M, Coan A, Herndon JE, and Abernethy AP. Prognostic significance of functional capacity and exercise behavior in patients with metastatic non-small cell lung cancer. *Lung Cancer*. 2012;76(2):248-52.
44. Jones LW, Watson D, Herndon JE, 2nd, Eves ND, Haithcock BE, Loewen G, and Kohman L. Peak oxygen consumption and long-term all-cause mortality in nonsmall cell lung cancer. *Cancer*. 2010;116(20):4825-32.
45. Wood WA, Deal AM, Reeve BB, Abernethy AP, Basch E, Mitchell SA, Shatten C, Hie Kim Y, Whitley J, Serody JS, Shea T, and Battaglini C. Cardiopulmonary fitness in patients undergoing hematopoietic SCT: a pilot study. *Bone Marrow Transplant*. 2013;48(10):1342-9.
46. Bouchard C, and Rankinen T. Individual differences in response to regular physical activity. *Med Sci Sports Exerc*. 2001;33(6 Suppl):S446-51; discussion S52-3.
47. Skinner JS, Jaskolski A, Jaskolska A, Krasnoff J, Gagnon J, Leon AS, Rao DC, Wilmore JH, and Bouchard C. Age, sex, race, initial fitness, and response to training: the HERITAGE Family Study. *J Appl Physiol*. 2001;90(5):1770-6.
48. Sisson SB, Katzmarzyk PT, Earnest CP, Bouchard C, Blair SN, and Church TS. Volume of exercise and fitness nonresponse in sedentary, postmenopausal women. *Med Sci Sports Exerc*. 2009;41(3):539-45.
49. Courneya KS, McKenzie DC, Mackey JR, Gelmon K, Friedenreich CM, Yasui Y, Reid RD, Vallerand JR, Adams SC, Proulx C, Dolan LB, Wooding E, and Segal RJ. Subgroup effects in a randomised trial of different types and doses of exercise during breast cancer chemotherapy. *Br J Cancer*. 2014;111(9):1718-25.
50. Carayol M, Bernard P, Boiche J, Riou F, Mercier B, Cousson-Gelie F, Romain AJ, Delpierre C, and Ninot G. Psychological effect of exercise in women with breast cancer receiving adjuvant therapy: what is the optimal dose needed? *Ann Oncol*. 2013;24(2):291-300.

51. Mishra SI, Scherer RW, Snyder C, Geigle P, and Gotay C. Are exercise programs effective for improving health-related quality of life among cancer survivors? A systematic review and meta-analysis. *Oncol Nurs Forum*. 2014;41(6):E326-42.
52. Thorsen L, Skovlund E, Stromme SB, Hornslien K, Dahl AA, and Fossa SD. Effectiveness of physical activity on cardiorespiratory fitness and health-related quality of life in young and middle-aged cancer patients shortly after chemotherapy. *J Clin Oncol*. 2005;23(10):2378-88.
53. Edvardsen E, Skjonsberg OH, Holme I, Nordsletten L, Borchsenius F, and Anderssen SA. High-intensity training following lung cancer surgery: a randomised controlled trial. *Thorax*. 2015;70(3):244-50.
54. Jarden M, Adamsen L, Kjeldsen L, Birgens H, Tolver A, Christensen JF, Stensen M, Sorensen VA, and Moller T. The emerging role of exercise and health counseling in patients with acute leukemia undergoing chemotherapy during outpatient management. *Leuk Res*. 2013;37(2):155-61.
55. Jarden M, Moller T, Kjeldsen L, Birgens H, Christensen JF, Bang Christensen K, Diderichsen F, Hendriksen C, and Adamsen L. Patient Activation through Counseling and Exercise-Acute Leukemia (PACE-AL)-a randomized controlled trial. *BMC Cancer*. 2013;13(1):446.
56. Hoffmann B. Feasibility of internet-based, physical training using the online platform 'OnkoActiv' in cancer patients-results of a pilot study. [Master Thesis]: Goethe University Frankfurt, 2014.
57. Jacobsen PB, Le-Rademacher J, Jim H, Syrjala K, Wingard JR, Logan B, Wu J, Majhail NS, Wood W, Rizzo JD, Geller NL, Kitko C, Faber E, Abidi MH, Slater S, Horowitz MM, and Lee SJ. Exercise and stress management training prior to hematopoietic cell transplantation: Blood and Marrow Transplant Clinical Trials Network (BMT CTN) 0902. *Biol Blood Marrow Transplant*. 2014;20(10):1530-6.
58. Steindorf K, Schmidt ME, Wiskemann J, and Ulrich CM. Physiologic and Molecular Mechanisms Linking Endurance and Resistance Training with Effects for Cancer Patients. *Deutsche Zeitschrift für Sportmedizin*. 2014;65:299-303.
59. Fiuza-Luces C, Soares-Miranda L, Gonzalez-Murillo A, Palacio JM, Colmenero I, Casco F, Melen GJ, Delmiro A, Moran M, Ramirez M, and Lucia A. Exercise Benefits in Chronic Graft versus Host Disease: A Murine Model Study. *Med Sci Sports Exerc*. 2013;45(9):1703-11.
60. Fiuza-Luces C, Gonzalez-Murillo A, Soares-Miranda L, Martinez Palacio J, Colmenero I, Casco F, Melen G, Moran M, Lucia A, and Ramirez M. Effects of exercise interventions in graft-versus-host disease models. *Cell transplantation*. 2013;22(12):2409-20.
61. Nieman DC. Exercise, upper respiratory tract infection, and the immune system. *Med Sci Sports Exerc*. 1994;26(2):128-39.
62. Barsevick AM, Irwin MR, Hinds P, Miller A, Berger A, Jacobsen P, Ancoli-Israel S, Reeve BB, Mustian K, O'Mara A, Lai JS, Fisch M, and Cella D. Recommendations for High-Priority Research on Cancer-Related Fatigue in Children and Adults. *J Natl Cancer Inst*. 2013;105(19):1432-40.
63. Koeppen S. Treatment of multiple myeloma: thalidomide-, bortezomib-, and lenalidomide-induced peripheral neuropathy. *Oncology research and treatment*. 2014;37(9):506-13.
64. Segal RJ, Reid RD, Courneya KS, Sigal RJ, Kenny GP, Prud'Homme DG, Malone SC, Wells GA, Scott CG, and Slovinec D'Angelo ME. Randomized controlled trial of resistance or aerobic exercise in men receiving radiation therapy for prostate cancer. *J Clin Oncol*. 2009;27(3):344-51.
65. Zedan AH, and Vilholm OJ. Chemotherapy-induced polyneuropathy: major agents and assessment by questionnaires. *Basic & clinical pharmacology & toxicology*. 2014;115(2):193-200.
66. Streckmann F, Kneis S, Leifert JA, Baumann FT, Kleber M, Ihorst G, Herich L, Grussinger V, Gollhofer A, and Bertz H. Exercise program improves therapy-related side-effects and quality of life in lymphoma patients undergoing therapy. *Ann Oncol*. 2014;25(2):493-9.

67. Wiskemann J, and Scharhag-Rosenberger F. Nebenwirkungsorientierte Behandlungspfade für die bewegungstherapeutische Betreuung onkologischer Patienten. *Bewegungstherapie und Gesundheitssport*. 2014;30(4):146-50.
68. Kremer LC, van Dalen EC, Offringa M, and Voute PA. Frequency and risk factors of anthracycline-induced clinical heart failure in children: a systematic review. *Ann Oncol*. 2002;13(4):503-12.
69. Khakoo AY, Liu PP, Force T, Lopez-Berestein G, Jones LW, Schneider J, and Hill J. Cardiotoxicity due to cancer therapy. *Texas Heart Institute journal / from the Texas Heart Institute of St. Luke's Episcopal Hospital, Texas Children's Hospital*. 2011;38(3):253-6.
70. Scott JM, Khakoo A, Mackey JR, Haykowsky MJ, Douglas PS, and Jones LW. Modulation of anthracycline-induced cardiotoxicity by aerobic exercise in breast cancer: current evidence and underlying mechanisms. *Circulation*. 2011;124(5):642-50.
71. Sturgeon KM, Ky B, Libonati JR, and Schmitz KH. The effects of exercise on cardiovascular outcomes before, during, and after treatment for breast cancer. *Breast Cancer Res Treat*. 2014;143(2):219-26.
72. Scott JM, Lakoski S, Mackey JR, Douglas PS, Haykowsky MJ, and Jones LW. The potential role of aerobic exercise to modulate cardiotoxicity of molecularly targeted cancer therapeutics. *Oncologist*. 2013;18(2):221-31.
73. Roodman GD. Treatment strategies for bone disease. *Bone Marrow Transplant*. 2007;40(12):1139-46.
74. Baker KS, Ness KK, Weisdorf D, Francisco L, Sun CL, Forman S, and Bhatia S. Late effects in survivors of acute leukemia treated with hematopoietic cell transplantation: a report from the Bone Marrow Transplant Survivor Study. *Leukemia*. 2010;24(12):2039-47.
75. Brawley LR, and Culos-Reed SN. Studying adherence to therapeutic regimens: overview, theories, recommendations. *Controlled clinical trials*. 2000;21(5 Suppl):156S-63S.
76. Winters-Stone KM, Dobek J, Nail L, Bennett JA, Leo MC, Naik A, and Schwartz A. Strength training stops bone loss and builds muscle in postmenopausal breast cancer survivors: a randomized, controlled trial. *Breast Cancer Res Treat*. 2011;127(2):447-56.
77. Rief H, Omlor G, Akbar M, Welzel T, Bruckner T, Rieken S, Haefner MF, Schlampp I, Gioules A, Habermehl D, von Nettelbladt F, and Debus J. Feasibility of isometric spinal muscle training in patients with bone metastases under radiation therapy - first results of a randomized pilot trial. *BMC Cancer*. 2014;14:67.

7 Appendix

7.1 Curriculum Vitae

Name:	**Rea Maria Kühl (Nies)**
Date of Birth:	13th of February 1981 in Braunschweig
Nationality:	German
Address:	Schroederstr. 49, 69120 Heidelberg
Phone:	+49 (0)6221-56-36180
Phone private :	+49 (0)176-40088494
E-Mail:	rea.kuehl@nct-heidelberg.de
E-Mail private :	rea.kuehl@web.de

Current position:	**Study Management and Coordination**
02/2011 -	PETRA-Study (Physical Exercise Therapy vs Relaxation in Allogeneic stem cell transplantation, RCT, ClinicalTrials.gov, no: NCT01374399): Patient recruitment with clinical cooperation partners, endurance and muscle strength measurement, questionnaires, exercise and relaxation sessions in clinical setting, exercise and relaxation counselling, ongoing care, study procedures, development of exercise and relaxation protocols and materials, ethics approval and grant writing, oversight of data entry, data evaluation. Division of Medical Oncology (Head: Prof. Dr. D. Jäger) and Preventive Oncology (Head: Prof. Dr. H. Brenner, former Prof. Dr. CM. Ulrich) Working group Physical Activity, Exercise and Cancer, Heads: Dr. Joachim Wiskemann and Prof. Dr. Karen Steindorf German Cancer Research Center (DKFZ) and National Center for Tumor Diseases (NCT), Heidelberg

02/2011 -	**Doctoral Student**
	Thesis: *Improving exercise prescriptions for hematological cancer patients during and after allogeneic stem cell transplantation – conclusions from two large RCTs.*
	Division of Medical Oncology and Preventive Oncology, National Center for Tumor Diseases (NCT), Heidelberg
	Mentors: Prof. Dr. G. Huber, Dr. Joachim Wiskemann

Education:

10/2005 – 09/2009	**Magister**
	Sport Science/ Prevention and Rehabilitation
	Magister Thesis: *Empirische Betrachtung der Zusammenhangsebene der körperlichen Leistungsfähigkeit und Fatigue bei Krebspatienten vor, während und nach allogener Stammzelltransplantation*.
	Department of Sport and Sport Science, University Heidelberg, Heidelberg, Germany
	Mentor: Prof. Dr. G. Huber
12/2007 - 12/2008	**Research Assistant**, Central Institute for Mental Health, Mannheim, Germany
	Exercise intervention study in allogeneic stem cell transplantation: Information sessions, measurement of endurance and muscle strength, questionnaires, supervision of exercise sessions in clinical setting, physical activity counselling, data entry
	Mentor: Dr. Joachim Wiskemann
10/2001 - 09/2004	**Training of nurses**
	St. Franziskus Hospital, Flensburg, Germany
2000	**Abitur (A-level)**
	Freie Waldorfschule Flensburg, Flensburg, Germany

Puiblications (peer-reviewed):

Kuehl R, Schmidt ME, Dreger P, Steindorf K, Bohus M, Wiskemann J. *Determinants of adherence in cancer patients during and after allogeneic HCT* (submitted to Med Science Sport & Exercise, 2015)

Wiskemann J*, Kuehl R,* Dreger P, Huber G, Kleindienst N, Ulrich CM, Bohus M. *Physical Exercise Training versus Relaxation in Allogeneic stem cell transplant patients (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.* (submitted to BMC Cancer, 2015) *shared first authorship

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. *shared first authorship

Scharhag-Rosenberger F, Kuehl R, Klassen O, Schommer K, Schmidt M, Ulrich CM, Wiskemann J*, Steindorf K*. *Exercise training intensity prescription in breast cancer survivors: validity of current practice and specific recommendations.* Journal of Cancer Survivorship, 2015. *shared last authorship

Kuehl R, Scharhag-Rosenberger F, Schommer K, Schmidt ME, Dreger P, Huber G, Bohus M, Ulrich CM, Wiskemann J. *Exercise intensity classification in cancer patients undergoing allogeneic HCT*. Med Science Sport & Exercise, 2015; 47(5):889-95.

Wiskemann J, Kuehl R, Dreger P, Schwerdtfeger R, Huber G, Ulrich CM, Jaeger D, and Bohus M. *Efficacy of exercise training in SCT patients – who benefits most?* Bone Marrow Transplantation, 2014; 49:443-8.

Other Publications (not peer- reviewed):

Wiskemann J, Nies R, Vandenbergh D. (2012): Kapitel 18 - *Leukämien und Lymphome*. In: Körperliche Aktivität und Sport bei Krebs. Baumann, Jäger, Bloch (Hrsg.) Springer, Heidelberg, 189-208.

Wiskemann J, Klassen O, Kühl R. *Cancer-related Fatigue. Sport als Therapieansatz gegen krebsbedingte Müdigkeit.* Medical Sports Network (02/2013).

Wiskemann J, Kühr L, Kühl R. *Evidenzbasierte Trainingsprogramme für Krebspatienten*. Onkologische Pharmazie (02/2012).

Congress attendance:

03/2015	ASORS Annual Meeting, Munich, Germany (poster presentation, talk)
05/2014	ACSM Annual Meeting, Orlando, USA (poster presentation)
07/2014	ECSS Annual Conference, Amsterdam, Netherlands (talk)
02/2014	German Cancer Congress, Berlin, Germany (invited talk)
02/2014	Annual Meeting working group "Spiroergometrie", Cologne, Germany (Young Investigator Award, 2. Prize/ poster, talk)
09/2012	dvs Meeting "Kommission Gesundheit", Leipzig, Germany (talk)
06/2012	International Symposium Physical Activity and Cancer, Cologne, Germany (talk)
02/2012	German Cancer Congress, Berlin, Germany (poster presentation)
10/2011	International Symposium Exercise and Cancer, Munich, Germany
10/2011	German Sports Medicine Congress, Frankfurt, Germany (poster presentation)
11/2010	International Conference Exercise, Energy Balance and Cancer (EEBC), Heidelberg, Germany

Conference Talks:

Determinanten der Trainings-Adherence und Kontrollgruppen-Kontamination in einer randomisierten, kontrollierten Interventionsstudie bei allogen stammzelltransplantierten Patienten. ASORS Annual Meeting, Munich (2015)

Can the ACSM's classification for exercise intensities be applied in hematological cancer patients receiving allogeneic stem cell transplantation? ECSS, Amsterdam (2014)

Sport und Bewegung bei Fatigue. German Cancer Congress, Berlin (2014).

Spiroergometrische Ableitung von Trainingsintensitäten bei Krebspatienten während und nach allogener Stammzelltransplantation. AG Spiroergometrie, Münster (2014)

The PETRA-Study: Physical Exercise Therapy and Relaxation in Allogeneic Stem cell transplantation. International Symposium Physical Activity and Cancer, Cologne (2012).

Einfluss des initialen Fitnessniveaus auf Trainingseffekte bei Patienten nach allogener Stammzelltransplantation. Annual Meeting dvs-Kommission Gesundheit, Leipzig (2012).

Poster Presentations (published peer-reviewed abstracts):

Validity of the ACSM's intensity classification in hematological cancer patients receiving allogeneic stem cell transplantation. Kuehl R, Scharhag-Rosenberger F, Schommer K, Ulrich CM, Wiskemann J. ACSM, Orlando, USA, 2014. [*Med Science Sport & Exercise*, 46(5): 1425, 2014]

Is the ACSM's classification of exercise intensities valid for breast cancer survivors? Scharhag-Rosenberger F, Kuehl R, Schommer K, Klassen O, Ulrich CM, Wiskemann J, Steindorf K. ACSM, Orlando, USA, 2014. [*Med Science Sport & Exercise*, 46(5): 538, 2014]

Fatigue in patients prior to allogeneic stem cell tranplantation. Is there utility for exercise interventions? Nies R, Bohus M, Dreger P, Schwerdfeger R, Jäger D, Ulrich CM, Huber G, Wiskemann J. German Cancer Congress, Berlin, Germany, 2012. [Cancer research clinical oncology, 138 (1): 60, 2012]

Physical performance status as independent predictor for cancer-related fatigue and physical functioning in allogeneic stem cell transplanted patients. Vandenbergh D, Bohus M, Dreger P, Schwerdtfeger R, Jäger D, Ulrich CM, Nies R, Wiskemann J. German Cancer Congress, Berlin, Germany, 2012. [Cancer research clinical oncology, 138 (1): 60, 2012]

Moderators influencing the impact of physical exercise on fatigue in patients undergoing allogeneic hematopoietic stem cell transplantation (allo-HSCT). Vandenbergh D, Bohus M, Dreger P, Schwerdtfeger R, Jaeger D, Ulrich CM, Kuehl R, Wiskemann J. ECSS, Bruges, Belgium, 2012. [Book of Abstracts: 234, 2012]

Psychophysische Konstitution von Patienten im Vorfeld der allogenen hämatopoetischen Stammzelltransplantation (allo-HSCT). Vandenbergh D, Nies R, Ulrich CM, Bohus M, Jäger D, Dreger P, Schwerdtfeger R, Huber G, Wiskemann J. DGEpi Jahrestagung, Mainz, Germany, 2011. [Abstractband: 589, 2011]

Modulation von Coping-Stilen durch körperliches Training vor, während und nach allogener Stammzelltransplantation. Nies R, O'Neill T, Ulrich CM, Bohus M, Jäger D, Dreger P, Schwerdtfeger R, Huber G, Wiskemann J. German Sports Medicine Congress, Frankfurt, Germany, 2011. [Deutsche Zeitschrift für Sportmedizin, 62, (7-8):218, 2011]

Psychophysische Konstitution von Patienten im Vorfeld der allogenen hämatopoetischen Stammzelltransplantation (allo-HSCT). Vandenbergh D, Nies R, Ulrich CM, Bohus M, Jäger D, Dreger P, Schwerdtfeger R, Huber G, Wiskemann J. German Sports Medicine Congress, Frankfurt, Germany, 2011. [Deutsche Zeitschrift für Sportmedizin, 62, (7-8):218, 2011]

Physical Exercise Therapy and Relaxation in Allogeneic Stem Cell Transplantation (PETRA-Study). A study design. Wiskemann J, Nies R, Huber G, Ulrich CM, Dreger P, Bohus M. EEBC, Heidelberg, Germany, 2010. [Conference Program: 30, 2010]

Prizes:

ASORS Best of Abstract 2015. Kühl R, Dreger P, Bohus M, Wiskemann J. *Determinanten der Trainings-Adherence und Kontrollgruppen-Kontamination in einer randomisierten, kontrollierten Interventionsstudie bei allogen stammzelltransplantierten Patienten.*

Young Investigator Award "AG Spiroergometrie" 2014, (2. Prize). Kühl R, Scharhag-Rosenberger F, Schommer, K, Ulrich CM, Wiskemann J. *Spiroergometrische Ableitung von Trainingsintensitäten bei Krebspatienten während und nach allogener Stammzelltransplantation.*

Poster Prize DKFZ PhD Student Retreat Weil der Stadt, 2013 (1. Prize). Kuehl R, Dreger P, Ulrich, CM, Huber G, Jaeger D, Bohus M, Wiskemann J. Topic: *PETRA-Study Design.*

Advanced Training:

02/2015	Transplant Academy, Komplikationen nach allogener Stammzelltransplantation, Hamburg
02/2014 – 03/2015	Sportpsychologische Handlungskompetenz in Prävention und Rehabilitation (asp), Kiel/Leipzig
02/2014 – 09/2014	SAS Online Course: Statistic: Introduction to ANOVA, Regression and Logistic Regression
10/2013	SAS Programming, SAS education, Heidelberg
05/2011 -	Teaching Seminar: Introduction to Epidemiology, NCT Heidelberg, (Prof. Dr. Steindorf)
04/2011 – 02/2014	Basic and Advanced Biostatistics Course, German Cancer Research Center, (Prof. Dr. Kopp-Schneider)
10/2011	Statistic Course: analysis of variance and regression, Freiburg
04/2011	Statistic Course: structural equation models, Freiburg
09/2010	Exercise therapy in cancer patients (DVGS), Heidelberg
02/2008 – 03/2008	Exercise therapy in cardiologic patients (DVGS), Heidelberg
04/2008	Medical Nordic Walking (DVGS), Heidelberg

7.2 Author Contributions

Manuscript I

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

JW, GH, MB conception, design, trial protocol; JW and RK supervision of exercise intervention and physical performance diagnostics; PD and RS study physicians; JW, RK and NK data management and statistical analysis; JW and RK drafted and finalized the manuscript, CMU and DJ revised the manuscript

Manuscript II

Physical Exercise Training versus Relaxation in Allogeneic stem cell transplant patients (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

JW, GH, MB conception, design, trial protocol; JW, RK, CMU initiation and implementation of the study; JW and RK conception and supervision of exercise intervention and physical performance diagnostics; RK study coordinator, endpoint assessments and exercise intervention; PD study physician; JW, RK and NK data management and statistical analysis; GH, MB, PD, CMU reviewed the manuscript, JW and RK drafted and finalized the manuscript

Manuscript III

Exercise intensity classification in cancer patients undergoing allogeneic HCT

RK, FSR and JW designed the research question, RK and KS performed assessment, RK and MES data analysis, PD study physician, GH, MB and CMU revised the manuscript, RK and FSR drafted and finalized the manuscript

Manuscript IV

Determinants of adherence and contamination in patients during and after allogeneic stem cell transplantation – outcomes from a RCT

RK and JW designed the research question, RK study coordinator, performs exercise intervention and assessment procedures, PD study physician, RK and MES data analysis, KS and MB revised the manuscript

7.3 Danksagung

Diese kumulative Dissertation wurde am Nationalen Centrum für Tumorerkrankungen (NCT) Heidelberg in der Arbeitsgruppe Bewegung, Sport und Krebs erstellt. Ich möchte allen danken, die Zeit und Energie aufgebracht haben, diese Arbeit zu ermöglichen und die PETRA Studie durchzuführen.

Allen voran möchte ich Dr. Joachim Wiskemann als herausragenden, immer verfügbaren und stets motivierenden Betreuer am NCT danken. Er gab mir die Möglichkeit die PETRA Studie als Studienkoordinatorin durchzuführen und mich in die Arbeitsgruppe Bewegung, Sport und Krebs am NCT einzubringen. Unsere Gespräche und Diskussionen habe ich immer als sehr wertvoll und konstruktiv empfunden.

Ich möchte mich bei Prof. Dr. Gerhard Huber bedanken, der diese Arbeit von Seiten des Instituts für Sport und Sportwissenschaft in Heidelberg betreut hat und bei Fragen stets zur Seite stand.

Ich möchte meinem PETRA Studienteam der letzten 4 Jahre danken. Insbesondere den Physiotherapeutinnen und Studienassistentinnen Tamara Christ und Petra Armbrust. Aber auch der tatkräftigen Unterstützung der medizinischen Doktoranden Dominik Vandenbergh und Benedikt Herzog sowie der Masterstudentin Belinda Hoffman bin ich zu Dank verpflichtet. Ohne sie alle wäre die Durchführung der PETRA Studie nicht möglich gewesen.

Ich möchte dem gesamten Universitätsklinikums-Allo-Team der Ambulanz, der Transplantations-Station *von Dusch* und der *Hämatologischen Intensiv Station (HIS)* für ihre Offenheit der Studie gegenüber danken. Weiterhin möchte ich der sportmedizinischen Abteilung des Universitätsklinikums danken, welche einen Großteil der spiroergometrischen Untersuchungen im Rahmen der PETRA Studie durchgeführt hat.

Mein besonderer Dank gilt natürlich allen Patientinnen und Patienten, die mir Ihr Vertrauen schenkten und an der PETRA Studie teilnahmen.

Ich möchte Dr. Friederike Scharhag-Rosenberger dafür danken, ihr herausragendes Wissen zur Spiroergometrie und Trainingswissenschaft mit mir zu teilen und mich im Rahmen des III Manuskriptes zu betreuen. Ich habe bei ihr immer eine offene Tür und kompetenten Rat zu allen Lebensbereichen gefunden.

Ich möchte Dr. Martina Schmidt für Ihre Hilfe und Diskussion zu allen methodischen Fragen und zum Datenmanagement danken. Prof. Dr. Karen Steindorf danke ich für ein immer offenes Ohr und Irmtraud Williams für das Korrekturlesen des Mantelteils.

Der gesamten Arbeitsgruppe Bewegung, Sport und Krebs möchte ich für die freundliche und hilfsbereite Arbeitsumgebung danken und natürlich auch für alle Aktivitäten außerhalb des NCTs.

Zuletzt möchte ich mich bei meinem Mann Sönke bedanken, der mich in jeder Phase der Arbeit unterstützt und motiviert hat und mir dadurch die Kraft gegeben hat, diese Arbeit zu einem erfolgreichen Ende zu bringen.

7.4 Erklärung

Erklärung gemäß § 8 Abs. 1 Buchst. b) und c) der Promotionsordnung

der Fakultät für Verhaltens- und Empirische Kulturwissenschaften

Promotionsausschuss der Fakultät für Verhaltens- und Empirische Kulturwissenschaften der Ruprecht-Karls-Universität Heidelberg
Doctoral Committee of the Faculty of Behavioural and Cultural Studies, of Heidelberg University

Erklärung gemäß § 8 Abs. 1 Buchst. b) der Promotionsordnung der Universität Heidelberg für die Fakultät für Verhaltens- und Empirische Kulturwissenschaften
Declaration in accordance to § 8 (1) b) and § 8 (1) c) of the doctoral degree regulation of Heidelberg University, Faculty of Behavioural and Cultural Studies

Ich erkläre, dass ich die vorgelegte Dissertation selbstständig angefertigt, nur die angegebenen Hilfsmittel benutzt und die Zitate gekennzeichnet habe.
I declare that I have made the submitted dissertation independently, using only the specified tools and have correctly marked all quotations.

Erklärung gemäß § 8 Abs. 1 Buchst. c) der Promotionsordnung der Universität Heidelberg für die Fakultät für Verhaltens- und Empirische Kulturwissenschaften

Ich erkläre, dass ich die vorgelegte Dissertation in dieser oder einer anderen Form nicht anderweitig als Prüfungsarbeit verwendet oder einer anderen Fakultät als Dissertation vorgelegt habe.
I declare that I did not use the submitted dissertation in this or any other form as an examination paper until now and that I did not submit it in another faculty.

Vorname Nachname
First name Family name _____

Datum, Unterschrift

Date, Signature _____