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Physical performance of allogeneic stem cell transplant candidates prior to transplantation

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Matthias Limbach

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Dean: Prof. Dr. Guido Sprenger
Supervisor: Prof. Dr. Joachim Wiskemann

„Dem Anwenden muss das Erkennen vorausgehen.“

Max Planck (1858–1947)

Danksagung

Den Weg bis hin zur Abgabe einer solchen Arbeit geht man nicht alleine. Er wird begleitet und mitgetragen von Familie, Freunden, Kollegen und einer ganzen Abteilung und Ihren Unterstützern, die eine gemeinsame Bestrebung und Passion teilen.

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ABSTRACT

Physical performance is not only a fundamental requirement for the activities of daily life, for family and work, but also for demanding phases of our lives, such as illness. There are substantial recommendations and statements for physical exercise to strengthen the physical performance in healthy individuals, for chronic diseases, but also specifically for various oncological diseases. For hemato-oncological patients, the disease itself, as well as the intensive treatment, represents a great challenge for physical resources. Even though methods of allogeneic hematopoietic stem cell transplantation (allo-HCT) have improved remarkably in recent years, intensive therapy requires patients to be in sufficient physical condition. Various tools have been developed for the assessment and risk stratification of patients in order to estimate the chances of the treatment. Various risk profiles can be illustrated, such as the presence of previous diseases or general comorbidities. However, in the past, modifiable risk factors such as low physical fitness (e.g. cardiorespiratory fitness) for higher symptom burden or worse outcome have also been identified. Against this background, physical exercise is becoming increasingly relevant and some exercise interventions during different phases of the disease are demonstrating promising health-effects. The evidence regarding the patient's health-status including physical performance and a successful implementation of exercise interventions prior to allo-HCT is still understudied.

The question arises whether *modifiable factors* exist, that can be identified and subsequently changed in order to improve physical performance and therefore the outcome of the hematological cancer-treatment. As before, further substantiated descriptions of this patient sample are necessary and too little is known about possibly modifiable and influencing factors prior allo-HCT.

Therefore, the aim of this dissertation is to contribute to closing this research gap. It investigates whether the main parameters of physical performance the cardiorespiratory fitness (CRF) and muscle strength are affected prior allo-HCT and their influencing variables. As a logical continuation of this question, the possibility of an exercise intervention shortly prior to allo-HCT in order to improve the physical performance in the short term is explored.

The first manuscript investigated CRF in allo-HCT candidates (n=194) and compared these data to healthy controls. Our results demonstrated a significantly decreased CRF in allo-HCT candidates prior transplantation. We found that higher Body Mass Index (BMI) values, low physical activity, amount of cardiotoxic agents and low hemoglobin-level before allo-HCT negatively impact CRF prior allo-HCT. On this basis, describing risk factors for low CRF before

allo-HCT could lead to a targeted approach to exercise intervention before rehabilitation that identifies patients with the greatest need.

The second manuscript examined muscle strength in allo-HCT candidates (n=212). Again, this parameter was shown to be decreased in allo-HCT candidates immediately prior transplantation and high deviations from a healthy reference population are revealed. We showed that especially younger patients of male gender and possibly with lower hemoglobin values are affected by muscle weakness. Our regression analysis showed, that muscle strength is significantly influenced by female gender, lower BMI, higher age and higher Hematopoietic Cell Transplantation-Comorbidity Index (HCT-CI) scores. In the context of increasingly older allo-HCT candidates, comorbidities (HCT-CI) should also be considered in the risk assessment. We assumed that future exercise interventions should focus on resistance training (RT) for the lower extremities, as they are more affected and play the main role in supporting and moving during weight-bearing tasks and daily activities.

The third manuscript, in turn, provided a research contribution to the question of whether pre-training - adopted shortly before the start of allo-HCT - can be feasible and effective. Due to low recruitment numbers, the study had to be terminated. This shows the limitations of the implementation method, but the training-specific content is promising. Despite of a very short time period, we were able to show that a high intensity interval training (HIIT) and a high-to moderate intensity RE is feasible and is able to improve physical performance. The obtained promising data on n=14 patients demonstrated significant effects on CRF, 6MWT performance, hand grip strength and patient-related outcomes (PROs). Obtained MVIC values show a positive trend. For future studies, it seems important to move the timing of recruitment further forward, in order to reach and include a larger number of candidates.

In summary, this dissertation adds to the body of research concerning hematological malignancies and the importance of a patients' health status prior allo-HCT. It provides comprehensive information about physical performance on the basis of CRF and muscle strength. We could demonstrate that these are already reduced in allo-HCT candidates shortly before the start of transplantation. The investigation of influencing factors of CRF and muscle strength contributes to a more precise identification of possible high-risk subgroups. This, along with the fact that exercise training just before allo-HCT seems to be feasible and effective, provides decisive information for future research, for the implementation of exercise programs and for individualized treatment strategies.

LIST OF SCIENTIFIC MANUSCRIPTS FOR THE PUBLICATION-BASED DISSERTATION

Manuscript I

Limbach, M., Kuehl, R., Dreger, P., Luft, T., Rosenberger, F., Kleindienst, N., Friedmann-Bette, B., Bondong, A., Bohus, M., Wiskemann, J. (2021). Influencing factors of cardiorespiratory fitness in allogeneic stem cell transplant candidates prior to transplantation. *Support Care Cancer*, 29(1):359-367. doi: 10.1007/s00520-020-05485-y. Epub 2020 May 4.

Manuscript II

Limbach, M., Kuehl, R., Köppel, M., Dreger, P., Luft, T., Bohus, M., Wiskemann, J. (2024). Factors affecting pretransplant muscle strength in allogeneic stem cell transplant candidates prior transplantation. Under review in *Supportive Care in Cancer* on February 08, 2024.

Manuscript III

Kuehl, R., Feyer, J., Limbach, M., Pahl, A., Stoelzel, F., Beck, H., Wegner, A., Rosenberger, F., Dreger, P., Luft, T., Wiskemann, J. (2023). Prehabilitative high-intensity interval training and resistance exercise in patients prior allogeneic stem cell transplantation. *Scientific Reports*, 13, 22069. doi.org/10.1038/s41598-023-49420-7. Epub 2023 December 12.

Contribution to studies:

This dissertation is based on two studies and compromises three manuscripts. Manuscript I and II are based on the PETRA Study, a randomized controlled exercise intervention trial in hematological cancer patients during and after allogeneic stem cell transplantation. The PETRA Study was conducted at the National Center for Tumor Diseases (NCT) Heidelberg in cooperation with the Heidelberg University Hospital (description see Chapter 2.1). The author of this dissertation performed the following work as part of the study: recruitment, informed consent, study inclusion, conducting assessments at the measurement time points, caring for patients during and after allo-HCT and conducting the exercise intervention, preparing the interim report, data collection and data analysis for the contents of Manuscript I and II, writing and submitting Manuscript I and II.

Manuscript III is based on the PRESENT-P study, a pilot exercise intervention study, with focus on the feasibility and safety of high-intensity endurance training and resistance training prior allo-HCT (description Chapter 2.2). The study was conducted at the National Center for Tumor Diseases (NCT) Heidelberg in cooperation with the Heidelberg University Hospital. The author of this dissertation performed the following work as part of the study: recruitment, informed consent, study inclusion, conducting assessments and supporting the writing process of Manuscript III.

1 General Background

Cancer is one of the challenges of our time, even though treatment prospects for oncological patients have improved considerably in recent decades. Supportive-therapy measures contribute to this in a very valuable way. Physical activity and exercise, as well as the physical performance status of patients, are now firmly established in the scientific perspective of the oncological research. One of these perspectives is directed at patients with *hematological* diseases. Specifically, patients undergoing allogeneic hematopoietic stem cell transplantation (allo-HCT) face a particularly high-risk and intensive treatment. Both the treatment itself and the accompanying consequences can have serious adverse health effects. A closer look at the treatment risks reveals that patients should have important prerequisites for the transplantation process. Several tools have been developed to identify patients at increased risk for complications, symptom-burden or to die from the treatment, which emphasizes the focus on the patient health status *prior treatment* with allo-HCT. Metrics emerge from a sports science perspective that are worthy of scientific investigation. For example, the physical performance parameters of *cardiorespiratory fitness* and *muscle strength* need to be considered more closely as comprehensive variables of patient status. These may be impaired by previous treatments or by the disease itself, but they seem to have an important predictive character for the outcome of allo-HCT. It becomes increasingly obvious that these two physical performance parameters should be as "strong" as possible prior treatment to minimize the risk of allo-HCT and thus may improve the chances for hematological patients.

In order to embed the dissertation in the current state of research and its scientific context, the following chapter briefly describes (Chapter 1.1-1.3): exercise oncology, hematological malignancies and allogeneic stem cell transplantation as a treatment option. To clarify the justification for research, the manifold physical limitations and burden of allo-HCT candidates are outlined in Chapter 1.4. At this, the physical condition *prior* to allo-HCT will be the priority, as this will be the focus of the remainder of this work. Nevertheless, it is important and also inevitable to deal with consequences and limitations that occur *during* or *after* the allo-HCT, if only because it is difficult to make a clear delineation of the intertwined processes. On the one hand, the aim is to illustrate the poor physical condition in which the

patients start treatment, but also the complications and risks that await them. Only then does it become clear how crucial it can be for patients to start treatment as "fit" as possible. Likewise, the first part of the thesis explains the risk estimation and the selection of allo-HCT candidates based on it (Chapter 1.5). To conclude this first part, Chapter 1.6 provides the state of the art of cardiorespiratory fitness and muscle strength impairments as well as pretraining for improving the physical performance prior allo-HCT. Research questions derived from this are formulated in the respective chapters (Manuscript I, II, III).

For reasons of comprehensibility of the research setting, a brief outline of the methodology of the PETRA Study (Physical Exercise Training versus Relaxation in Allogeneic stem cell transplantation)[1] and the PRESENT-P Study (Pre-Exercise for allogeneic stem cell transplant patients: a pilot study), as well as the main assessment methods of cardiorespiratory fitness (CRF) and muscle strength is given (Chapter 2).

In Chapter 3-5 the articles published as part of this dissertation are presented: 1. The identification of potential influencing factors immediately prior allo-HCT of *cardiorespiratory fitness.* 2. The identification of potential influencing factors immediately prior allo-HCT of *muscle strength*. 3. The investigation of the feasibility and preliminary efficacy of a high intensity interval training (HIIT) and moderate to high-intensity resistance exercise (RE) to increase physical performance in patients prior allo-HCT.

This is followed by the general discussion (Chapter 6) including the summarized research findings, relating the knowledge gained, addressing existing limitations as well as future directions.

1.1 Exercise Oncology

Physical activity, exercise or exercise therapies have become an integral part of oncology research. Higher levels of physical activity are associated with a lower risk of several cancers. For colon, breast and prostate cancer, the evidence base is very high, whereas for myeloma and hematologic cancer the evidence is limited. There are now condensed evidence-based strategies both for primary prevention of cancer, but also for addressing adverse side effects and consequences of cancer itself, as well as during and after treatment. The evidence for these cancer-related health outcomes varies. Strong evidence exists, for example, for improved perceived physical function, higher quality of life (QoL), or reduced cancer-related fatigue[2-4]. In addition, there is increasing evidence that the prognosis and the survival are also related to the degree of physical activity. Epidemiologic evidence demonstrates that the relative risk of death from breast, colon, and prostate cancers, for

example, can be reduced by 40-50% depending on activity levels. Such evidence also exists for hematologic diseases, however it is still limited. Interestingly, a possible separate indicator of physical activity, cardio respiratory fitness, appears to be associated with higher survival after cancer diagnosis[5, 6]. Molecular biological mechanisms regulating metabolism and systemic immune function are partly responsible for the beneficial effects and impact of physical exercise respective in general physical activity[4, 7].

General recommendations suggest to avoid "inactivity" and aim for a global high level of physical activity (150 minutes of moderate physical activity per week or at least 75 minutes of vigorous physical activity per week) with 30 minutes of aerobic activity three times per week and strengthening exercises for the major muscle groups at least at two days per week[2, 3, 8]. Due to increasing research, it is possible, although still limited, to make specific statements about modalities of physical exercise (FITT-criteria: frequency, intensity, time, type) with respect to cancer-related health outcomes. Thus, depending on these outcomes, suggestions can be found on frequency (sessions per week), intensity, type (resistance and aerobic or combination), and time (duration). In some cases, information on dose-response can also be provided[2].

In summary, "*exercise is medicine in oncology*"[3] and physical activity, exercise, or exercise therapies are indicated for primary prevention of cancer as well as the continuum of cancer treatment and for cancer survivors[5, 9-11]. Endurance and strength training are recommended, although recommendations for targeted therapies are limited. We still need a better understanding of existing effects and outcomes[12] and more evidence for personalized exercise interventions, including for hematologic malignancies.

1.2 Hematological malignancies

When it comes to the question, which cancer requires allo-HCT, one has to look particularly at hematological malignancies. These cancer types affect the hematopoietic system and are a heterogeneous group of neoplasms of clonal origin developing from hematopoietic tissue or bone marrow and reticular tissue[13]. The most common primary diseases to mention are mainly described in this chapter.

Overall, it can be noted that hematologic malignancies account for 8-9% of all incident cancers and the incidence increased since the 1960s[14]. They represent 6.5% of all cancers types worldwide and more than 50% of affected patients are over 65 years of age[15]. According to the World Health Organization (WHO) Framework Agreement (2008), a proposal is made to categorize hematologic and lymphatic diseases and to present a global consensus for diagnosis. In this context, the entire spectrum of neoplasms of the

hematopoietic and lymphoid tissues becomes clear[16]. However, the variety of hematologic disorders requires a specific selection of the most common diseases. Usually, a classification is made according to the four subtypes: Leukemia, Hodgkin lymphoma (HL), non-Hodgkin lymphoma (NHL), and multiple myeloma (MM)[17]. These can generally be classified as lymphoid or myeloid according to the origin and pathogenesis of the tumor in the hematopoietic or lymphoid tissue[13]. Hematological malignancies also include myeloproliferative and myelodysplastic syndromes (MDS)[18]. This selection corresponds to the existing diseases in the present study population and also provides an indication for allo-HCT.

There are various forms of blood cancer with different courses of disease and symptoms. The four most common leukemia are classified as "acute myeloid leukemia (AML)", "chronic myeloid leukemia (CML)", "acute lymphoblastic leukemia (ALL)" and "chronic lymphocytic leukemia (CLL)". However, there are other subtypes, which are considerably less common[16]. Regarding lymphomas, subtypes can also be defined. The most relevant distinction is between HL and NHL. The latter are further subdivided into low-malignant and high-malignant lymphomas and, depending on the cell series involved, into B- and T-cell lymphomas. The group of low-malignant B-cell - non-Hodgkin lymphomas includes MM (syn. plasmocytoma), one of the most common tumors of the bone or bone marrow.

1.3 Allogeneic stem cell transplantation

The allo-HCT has evolved from a treatment of “ultima ratio” in otherwise hopeless cases to an indicated therapy and has its established standing within hematology and oncology[19]. In the past decades the number of allo-HCT performed has continued to increase. In total, about 50.000 transplantations are performed worldwide, in Europe about 18.000 and in Germany the numbers are on a comparatively high level at about 3.300 transplantations per year. This has been contributed by an expanded availability of donors, but also by improved transplantation techniques such as reduced-intensity conditioning (RIC) or a better use of the immunotherapeutic Graft-versus-leukemia-effect (GVL) as well as improved supportive measures. Current data show an overall mortality in the measured period of 2013-2017 of approximately 40%. Although mortality rates continue to decrease, patients are thus at higher risk of non-relapse mortality (NRM). This remains at a considerable level despite a decrease from 41% to 26% in the years from 1993-1997 and 2003-2007[20] .

There are various indications for allo-HCT, depending on the disease and its course on the one hand, and on the individual risk constellation on the other hand. As stated above, in principle, malignant hematological diseases such as ALL, AML, MDS, CML, CLL,

Osteomyelofibrosis (OMF), lymphomas (HL and NHL, primary with a high degree of malignancy or after relapse) and MM are indicated[19]. However, non-malignant hematologic diseases such as severe aplastic anemia (SAA)[21] or others are also indicated. Often, allo-HCT is also the treatment of choice for patients when other therapies and treatments have failed or there has been a relapse. Thus, patients have often already undergone various therapies *prior* allo-HCT[19], leaving them in weak health status before the upcoming crucial treatment.

At the beginning of allo-HCT is the conditioning treatment (high-dose chemotherapy and, if necessary, total body irradiation). The aim of this treatment is to create a myeloablation and thus to enable the donor stem cells to settle. More recently, nonmyeloablative regimes were used in weaker, older and medically debilitated patients[22]. Immunosuppressive treatment is necessary to prevent rejection of the transplant. On day 0, the actual transplantation takes place, followed by the engraftment. Overall, especially the time up to *180 days after allo-HCT* is associated with many complications, consequences and risks of the therapy and the underlying disease itself[19].

Almost 50% of the long-term survivors suffer from moderate to severe impairment on exercise capacity respective cardiorespiratory fitness (CRF)-values and almost 40% from general physical deconditioning, one year after the therapy. This results in reduced QoL, higher fatigue values and disability[23].

Relapse of the underlying primary disease and Graft versus Host Disease (GvHD) are the most common causes of death. Other causes of mortality are secondary malignancies, followed by infections, bacterial, viral or fungal infections which frequently damage various organs (e.g. liver, kidney and lungs) or the occurrence of severe respiratory and cardiovascular disease[24-28].

Compared with the general population, the mortality rate is 4 to 9 times higher than expected for at least 30 years after transplantation. Thus, life expectancy is approximately 30% lower regardless of current age[29]. However, it must be critically noted here that therapy is continuously subject to change and therefore the prognosis and statistics also fluctuate. For example, RIC-protocols result in a different risk model[30].

1.4 State of the Art: main consequences of disease and treatment

This chapter will serve as a foundation for the later research questions. As described, allo-HCT is a curative therapy for various hematologic diseases, but it is also a high risk due to the intensity of the therapy and many potential therapy-related side effects. The decision to proceed with allo-HCT, is complicated by several factors, including potential transplant-

related mortality (TRM), disease heterogeneity and patients preferences. Presumably, the risk and potentially complications depend on *the preparatory measures before treatment*, such as the choice of a suitable donor, the patient's age, the timing of the allo-HCT or the individual pre-existing comorbidity burden of the patient[31]. In this dissertation, the health status of patients is of primary importance, as it is directly related to cardiorespiratory fitness and muscle strength - the main focus of this thesis. The following section provides a perspective on some of the main consequences faced by patients *before*, *during* and *after* allo-HCT: anemia, cancer-related fatigue, neutropenia and leukozytopenia, bleeding, psychological problems, GvHD, physical deconditioning, late complications as well as long-term complications. This section provides a rationale for why patients should, at best, be in strong physical condition to be prepared for the stresses ahead.

ANEMIA is often associated with hematologic or lymphatic disorders. The prevalence of anemia at diagnosis of CLL, NHL, and HL is estimated to be nearly 25%, about 50%, and 37.4%, respectively. Thus anemia can be prevalent even before chemotherapy is started[32-34] with potentially consequences in physical functioning[35]. The decreased oxygen capacity of blood in cancer patients impairs QoL, survival, and potentially response to treatment with chemotherapy or radiation[34, 36]. Affected patients show symptoms of general weakness and dizziness, shortness of breath, possess a higher risk of cardiac arrhythmia[37] or reduced performance capacity[38, 39]. Thus, the goal in supportive care is to raise hemoglobin (Hb) levels. Increasing Hb-levels not only correct anemia and thus improve physical performance as well as QoL, but may also optimize clinical outcome parameters in general[34]. Nevertheless, treatment of cancer patients with recombinant erythropoietin (EPO) remains controversial and the use of erythropoiesis-stimulating agents must also be weighed against the risks[40]. Factors intrinsic to disease, such as inadequate erythropoiesis, and treatment-related factors, such as repeated treatment with red blood cell transfusions due to anemia in MDS and AML patients, could lead to systemic iron overload with further multiple health consequences. It is reported, that high pre-transplant ferritin levels are associated with an increased risk of invasive fungal pneumonia, which can further debilitate transplant candidates[41]. On the other hand, a meta-analysis shows that fatigue, for instance, can be significantly reduced with erythropoietin[42] and it appears to be safe, effective and well-tolerated[37]. From the current guidelines, erythropoiesis-stimulating agents for therapy of anemia are suggested only for selected patients due to safety concerns regarding tumor growth and increased risk of cardiovascular events[40, 43]. The management of anemia and the specific symptoms is essential for exercise strategies and must be considered in their planning (e.g. Hb-level ≥7.0 g/dl).

Somatic problems are usually multiclausal, and physical performance may be affected by more than just anemia. Also, symptoms are mutually dependent or amplify each other in a "symptom-enhancing effect". Thus, the symptom of fatigue could be also associated with anemia[34].

CANCER-RELATED FATIGUE is one of the most common and burdening consequences of cancer therapies and the disease itself. The most commonly described clinical symptom of cancer-related fatigue is a feeling of tiredness, exhaustion, and lack of energy. There is loss of motivation as well as memory and concentration deficits. Affected patients describe the symptoms differently. A key feature is that cancer related fatigue- symptoms do not improve significantly after rest and sleep[44]. Cancer-related fatigue affects the QoL and is discussed as a risk factor for reduced prognosis and survival[45]. Furthermore the symptoms could negatively impact daily activities and daily activity level[46] , with the possible known deconditioning effects (see below). In hematological malignancies, cancer-related fatigue is also a highly prevalent symptom and plays an essential role. In patients with AML it has been shown that severe fatigue even prior to remission induction chemotherapy may be a prognostic factor for shorter overall survival (OS). This effect was found to extend beyond known clinical prognostic factors such as age, performance status and cytogenetic risk[47]. The prevalence and clinical course of cancer-related fatigue are well studied, but the underlying mechanisms and the complexity of biological, physiological, molecular and psychological factors involved are not fully understood[48]. Among other factors, inflammatory processes have emerged as an important biological pathway for cancer-related fatigue. Thus, studies show associations between inflammatory markers and fatigue, also in individuals undergoing allo-HCT including high-dose chemotherapy[45, 49]. These processes can be detected during and especially after treatment. The subjective experience of cancer-related fatigue is highly variable and cannot be explained by disease- or treatment-related characteristics, suggesting that host factors play an important role in the development and maintenance of this symptom. Longitudinal studies indicate that genetic, biological, psychosocial, and behavioral risk factors for cancer-related fatigue may play an important role. As with the other side effects, fatigue occurs as a multifactorial problem and there is currently no gold standard for treatment. But there are treatment-approaches that have a positive impact on cancer-related fatigue and some are established in supportive care. A large number of intervention studies, also randomized controlled trials (RCTs) show that physical activity and exercise-based interventions are most promising and recommended as first-line treatment for cancer-related fatigue[45], also in hematological patients but with lower evidence-level[50-52], followed by psychological und pharmacologic therapies[53].

Again, it is obvious that somatic problems can be multiclausal and caused due to intensive treatment protocols or the disease itself.

NEUTROPENIA and *LEUKOCYTOPENIA* are another example of the additional challenges that lead to a compromised health status in hematology patients. They cause patients to be exposed to an increased risk of infection, making them susceptible to bacterial or viral diseases, especially in patients with AML or CLL. Patients with AML have qualitative and quantitative deficits in granulocytes that may predispose them to bacterial and fungal infections. In ALL, there are qualitative deficits in lymphocytes, resulting in hypogammaglobinemia and decreased cell-mediated immunity that predisposes to certain bacterial, viral, and fungal infections. Chemotherapies often exacerbate these deficits, leading to prolonged periods of severe neutropenia and disrupting mucosal barriers, further increasing the risk of infection[54]. Furthermore, patients with hematological diseases, especially MDS or acute leukemia, suffer from prolonged or intermittent febrile episodes, including neutropenia, which may be associated with suppressed inflammatory responses. This further compromises the QoL and health status of patients[55, 56]. In addition, most likely the increased risk of infection leads to further isolation of patients, further limiting activity levels. These limitations have immediate physiological consequences and can reinforce each other in a kind of downward spiral, leading to a vicious circle of reduced physical activity and reduced physical performance. This is often described in oncological diseases, but is particularly pronounced in patients with hematological cancer[57].

BLEEDING: Since hematologic diseases are characterized by ineffective hematopoiesis and morphological abnormalities of hematopoietic cells and are consequently accompanied by thrombocytopenia, bleeding is a significant complication in recipients of allogeneic hematopoietic stem cell transplants[58, 59]. The risk of bleeding limits various activities, including physical activity or physical exercise. Patients must be cautious during physical exertion. Therefore, thrombocytopenia is also listed among the relative or absolute contraindications[58]. Bleeding events must be taken seriously and may affect the survival of allo-HCT-recipients. Patients with these major risk factors for bleeding have special attention: myeloablative conditioning, cord blood transplantation, severe thrombocytopenia after day +28 and the development of acute GvHD grade III-IV, or patients diagnosed with graft-associated microangiopathy and anticoagulation[60]. In general, a platelet count of <10.000/µL and <20.000/µL should be maintained[58, 61]. There are no clear recommendations on contraindications to exercise training in the presence of low platelet counts. The previous

recommendations are basic empirical values. It is important to consider the platelet count with respect to the training modalities and adjust training accordingly. Primarily, patients with platelet counts of <20.000/μL should be treated with caution. However, under therapeutic supervision, training is considered safe and feasible. Patients should always be monitored closely for signs of bleeding during exercise[58].

PSYCHOLOGICAL PROBLEMS: Relatively high prevalence of psychological problems can also be observed in patients without previous psychiatric disorders. For example, depressive symptoms (approx. 35%), delirium (approx. 35%) or post-traumatic stress disorder (approx. 20%) may occur before, during or after treatment with allo-HCT. Neurocognitive dysfunctions caused by various chemotherapeutic agents (busulfan or fludarabine) are also among the psychological impairments. Psychological distress can be associated with some outcome parameters and higher symptom burden[62]. This highlights the importance of targeted attention and treatment.

THE GRAFT VERSUS HOST DISEASE: The GvHD is triggered when the donor's T cells act against the cells of the immunocompromised recipient because the histocompatibility antigens do not match[63]. GvHD is affecting an increasing number of long-term survivors[64]. A classification is made between *acute* GvHD (aGvHD), which develops in the early phase (in the first 100 days after transplantation), *late-onset acute* GvHD (more than 100 days after transplantation) and *chronic* GvHD (cGvHD), which can develop any time post transplantation (manifestation from aGvHD, after treatment of aGvHD or de novo). Cases of GvHD with features of both chronic and acute GvHD are referred to as *overlap syndrome* or *acute on chronic* GvHD with a manifestation any time post transplantation. *Acute* GvHD develops in 25-75% of patients. It affects the skin, liver and the gastrointestinal tract. Depending on the severity and number of organs affected, it is classified into grades I-IV, with grade IV causing the highest mortality rate. Severe GvHD (grade III-IV) is associated with adverse prognosis, with 25% long-term survival for grade III and 5% for grade IV[31, 63, 65].

The cGvHD is reported with an incidence of 40% to 70%[66]. It is one of the most common and serious late complications of allo-HCT, including a severe and life-threatening liver disease[63, 67]. But the cGvHD has also diverse clinical manifestations including muscles, fascia, joints, heart, morrow (anemia, thrombocytopenia, and neutropenia), lungs and other[25, 63]. In addition, clinically significant fatigue symptoms are reported more frequently in patients with cGvHD than in unaffected patients[68]. Systemic corticosteroid therapy is recommended as the standard and first-line therapy for cGVHD. However, less than 40-50%

of patients respond positively to this treatment. Secondary- and tertiary treatments are also not very successful[64]. The toxic side effects of the treatment (immunsupressive agents, steroids) are critical. Chronic immunosuppressant therapy can cause for example diabetes, muscle weakness, osteoporosis or vascular necrosis[63]. It becomes apparent, that in addition to the life-threatening consequences of GvHD, there is also a significant adverse impact on physical function and QoL. Exercise therapy offers an approach for treatment and improves the multiple physical deficits of patients with GvHD[61].

DECONDITIONING: The above-mentioned consequences and impairments can already occur during the acute phase of treatment and illness. An increased patient-reported symptom burden under isolation conditions during the inpatient phase and after discharge was associated with a decrease in physical activity[69]. This is also illustrated by the following figure 1 of our own data, in which activity behavior (accelerometer; steps per day) is related to the allo-HCT-treatment and the decrease in various blood parameters (Hb, platelets, leukocytes) in the inpatient phase compared to the days before allo-HCT[70].

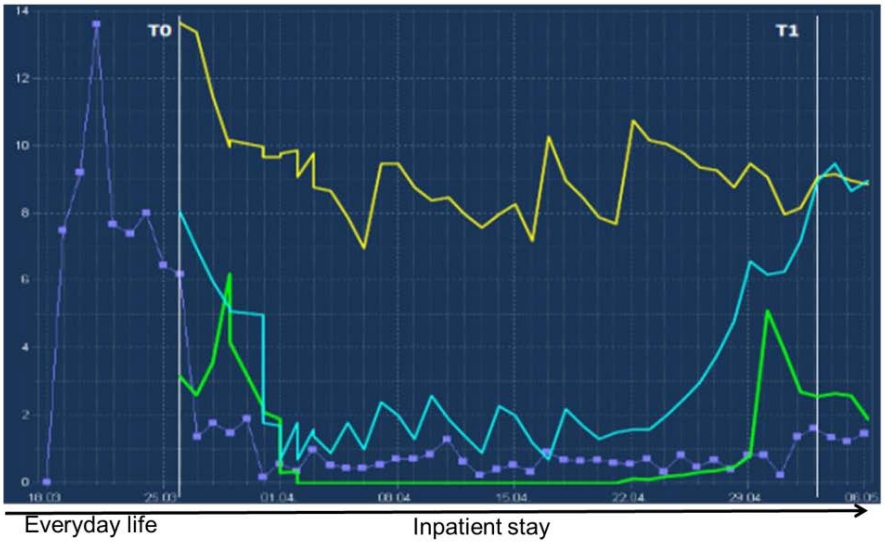

Figure 1. Case report: movement behavior in the context of allo-HCT. Hemoglobin (yellow), platelets (blue), leucocytes (green), steps per day (purple).

Further physical deconditioning is associated with the phase of immobilization. This can be determined, among other things, by a reduced muscle strength and CRF of the patients. Cause of the lack of physical activity is the changed environmental condition of the inpatient setting and the deteriorated general condition. The long inpatient stay of weeks and the isolation during the conditioning and aplasia phase, where patients stay mainly in their room, limit the patients' range of motion. But these conditions are also possible due to

various treatments prior to allo-HCT. The manifold effects of physical inactivity on cardiac output, oxidative capacity or other physiological processes[71] and on the musculature are also known from bed rest studies. Due to the prolonged bed rest, patients are additionally confronted with degenerative processes of the musculature, tendons or also with deficits of the neuronal control. In "bedrest" studies, as simulated weightlessness of space research, the changes in the musculature in the form of loss of strength and atrophy in response to prolonged bed rest have been demonstrated [72]. Boer and colleagues, as well as the Gruther research group, also showed that after "bedrest", degenerative processes of the musculature begin after only a short period of time[73, 74]. "Bedrest"-induced loss of muscle mass is evident and directly related to reduced mobility and worsened functional status leading to a loss of coping with everyday tasks[75].

LATE COMPLICATIONS AND LONG-TERM COMPLICATIONS: As a result of the intense treatment, various late complications and long-term complications may occur. They are manifold and affect the endocrine[76] and metabolic system (e.g. diabetes or osteoporosis) and muscular or connective tissue. Pulmonary, neurological or gastrointestinal complications as well as cardiac complications have also been reported[25, 77]. But also the immune system or the hematopoietic system can be affected[77]. A study summarizes the effects on the different domains of QoL (physical functioning, emotional functioning, social functioning, role functioning and overall QoL). The findings demonstrate statistically and clinically significant adverse impact of allo-HCT on QoL. At least 25% of survivors continue to have troublesome symptoms, even years after allo-HCT[78]. Late complications of allo-HCT remain a complex field. Despite steady improvements over the past decade, the management of these complications still represents a major challenge and burden for both patients and providers. Early diagnosis of late complications is important to achieve optimal outcomes[77].

As this chapter describes, hematological patients are faced with a major challenge due to the allo-HCT-related impairments or the disease itself. Although there are recommendations to reduce the individual suffer and symptoms in a specific way, e.g. through exercise interventions, many resources are required of patients.

1.5 State of the Art: Risk estimation and selection of appropriate patients for allo-HCT

It is important to know which subgroups are most affected by certain complications and can expect a difficile course of treatment. Therefore, a well-founded risk assessment is

necessary. Assessments of "who is fit" for allo-HCT[79] are done in a variety of ways. Different baseline factors have to be considered. These include, for example, disease characteristics such as disease status or cytogenetic abnormalities, but also patient-specific criteria. The risk factors of allo-HCT cannot be clearly separated for the phases of *pre*transplantation, transplantation and *post*transplantation. Rather, the risk factors for each stage influence and also affect each other. For example, the choice of transplant protocol affects the incidence and severity of GvHD or infection – that is, the outcome of allo-HCT.

Therefore, the selection of patients suitable for allo-HCT must be done very carefully. Recommendations are available on which criteria should be used to evaluate the suitability of patients prior to transplantation. These recommendations include: clinical evaluation, laboratory evaluation, end-organ assessments and the assessment of consultative services (e.g. nutritional assessment, psychosocial criteria)[80]. This leads to a possible risk stratification, categorized in "good-risk" candidates and "high-risk" candidates[79].

Maximizing the benefit of allo-HCT, while minimizing the risk for associated complications, remains the greatest challenge in the field. This challenge has led to the development of several prognostic scoring systems over the past two decades and various prognostic models have been established to predict the risk of allo-HCT[81].

In general, scores or scales are used to assess the performance status of oncology patients in order to be able to make more informed statements about the prognosis, but also to better plan therapy goals or treatments. Examples are the Karnofsky Performance Status (KPS)[82], which was developed to evidence of disease, to measure self-care and daily activities or the Eastern Cooperative Oncology Group (ECOG) scales. However, these cannot be adopted entirely uncritically, as conclusions about specific and individual patient assessments are subject to a high margin of error[83, 84].

In the meantime, there are various approaches for risk stratification of allo-HCT candidates. Various assessment tools are used to try to predict the patient-specific risk on the basis of different variables. The developed scores are expected to help in balancing the risk-benefit ratio and to improve an optimal decision-making process for transplantation. Furthermore, the probability of success of transplantation could be enhanced with these tools. Among the tools can be identified the Comprehensive Geriatric Assessment (CGA), the Disease Specific Risk Assessment Models (Disease Risk Index - DRI) and the Predict all-cause Mortality Score (PAM). However, these scores have not gained significant acceptance. The majority of the tools used are as follows.

The European Society for Blood and Marrow Transplantation (EBMT) introduced a five-component pre-transplant risk scoring system for patients with CML as early as 1998. The EBMT score was also tested in patients with various other hematological diseases. The EMBT score also finds a relatively wider range of use, certainly also due to the simplicity of use. Furthermore, the validation was carried out on the basis of some studies, which includes heterogeneous study populations and thus underlines the representatively[85]. Analyses show an association of the EBMT risk score and the mortality without relapse, the risk of relapse and the survival after allo-HCT for AML, ALL, MDS, MPS, NHL, MM, and AA[86]. Altogether, it was demonstrated that the score can estimate risk of mortality after allo-HCT, but nevertheless this score is also associated with some obscurities, which does not allow an uncritical use[85]. However, the EBMT Score helps in risk assessment and provides important information for the transplantation process.

In the context of an aging population and increasing numbers of cancer patients, comorbidity management will become increasingly important. In general, it should be noted that comorbidities can affect frailty, functional status, and also outcome. Furthermore, the presence of various comorbidities has a relevant impact on cancer-treatment[87]. Consequently they are under very special consideration in the risk assessment of allo-HCT candidates. To improve the risk assessment with focus of comorbidities for the transplantation process prior to allo-HCT, the Hematopoietic Cell Transplantation-Comorbidity Index (HCT-CI) was developed. This was created on the basis of another nontransplant index, the Charlson comorbidity index (CCI), that has been previously demonstrated as useful for predicting outcomes in patients prior allo-HCT. However, there were methodological limitations regarding the sample size and study population and the differentiation of comorbidities. The new approach now takes into account a differentiated and specific approach regarding comorbidities, also based on laboratory data. Individual comorbidities were weighted according to their prognostic significance in Cox proportional hazard models. Consideration was initially given to laboratory data, pulmonary function, Left Ventricular Ejection Fraction (LVEF), and levels of bilirubin and hepatic Transaminases were included in the definitions of pulmonary, cardiac, and hepatic comorbidities, respectively. Second, all comorbidities that occurred in the studied population of HCT recipients were included in a risk assessment analysis. On this basis, the impact of specific comorbidities on NRM and survival was then weighted and a new tool for predicting outcomes and stratifying allo-HCT candidates was created[85, 88]. Based on this, more specific analyses exist for entity-adjusted risk assessments using the HCT-CI and HCT-CI/age for example, for AML and MDS[89].

The HCT-CI is divided into the following categories: low (0), intermediate (1-2), and high (3). The specific procedure for determining HCT-CI is described in the guidelines[90]. Furthermore, a web-based application for the calculation of the score is available at: http://www.hctci.org/Home/Calculator.

So far, there is no comprehensive tool that performs comprehensive predictions. Thus, a combination with other variables and scores is recommended and used in practice. Sorror and colleagues also conclude that the HCT-CI and KPS should be assessed simultaneously before HCT. The combined use of both instruments likely improves risk stratification for HCT outcomes[91]. In summary, based on the expert consensus, the assessment of eligibility for allo-HCT is complex, multifaceted and a multidisciplinary process. In the evaluation, disease-related factors such as diagnosis, remission status, DRI, but also patient-related factors including physiological factors such as age, KPS, HCT-CI or Frailty Score, but also psychosocial and economic parameters have to be considered[80, 92].

It should be noted that many relevant factors prior to HCT are "*given*" that *cannot be changed*. The type of disease, the age of the patient, or genetic determinants cannot be influenced. Of course, this also applies to most concomitant diseases. It can be concluded that the various allo-HCT prognostic systems are important for risk stratification, but individual prediction remains a challenge[93].

Ultimately, the decision to proceed with transplantation remains a multidisciplinary one[94]. Concentrating on factors that *can be changed* brings into focus a complementary approach taken by the author's Wood et al., who demonstrated that the CRF (VO_{2peak}), a potentially modifiable variable, prior allo-HCT has prognostic value[95]. Furthermore, it is suspected that the combination of variables, including muscle mass, muscle strength, and also the CRF (VO_{2peak}) may have high relevance for risk stratification[96].

1.6 State of the Art and research questions of the manuscripts

The following chapter addresses the scientific state of the literature regarding the main topics of this dissertation. It highlights CRF and muscle strength as possibly relevant factors for hematological patients prior to allo-HCT and gives a specific scientific background to previous research results on the topic of pretraining in the context of allo-HCT-candidates.

1.6.1 State of the Art Impairments of CRF: What's the risk?

For different clinical questions and indications, CRF can help to estimate the risk in various patients and is considered to be a predictive value for survival[97, 98]. CRF values are an independent predictor of numerous chronic diseases, and there is probably also an

association with cancer incidence or survival after a cancer diagnosis[99]. Thus, CRF can be identified as a predictive variable in advanced lung cancer[100] or breast cancer[101] . In general, impaired CRF is measured in various cancer patients and the values are reduced compared with age-matched and gender-matched normative values for sedentary individuals. This apparently was even the case when patients were classified with a good functional status (KPS ≥70; "good" LVEF ≥50%; cohort 130 operable breast cancer patients)[71]. Good clinical practice attempts to assess cardiopulmonary function by determining e.g. LVEF, pulmonary function tests including forced expiratory volume in one second (FEV1) and diffusion capacity of the lungs for carbon monoxide (DLCO) prior allo-HCT. While assessments like these detect limited functional systems and therefore vulnerable candidates prior allo-HCT[102-104], they are also critical because they only examine the functional systems at "rest" and not under "exertion". Therefore, they do not represent the entire integrative system of CRF (see Chapter 2.3). Thus, impairment of cardiac function may still be present even if "classic" functional testing is without findings. In this respect, parameters such as VO_{2peak} are of great importance for risk stratification[102, 105]. A cardiopulmonary exercise test (CPET) with the estimation of VO_{2peak} may identify further potentially vulnerable subgroups, also prior allo-HCT[102].

CRF seems to be multifactorial affected, although the various underlying mechanisms are not fully understood. Impairments may occur in one organ or simultaneously in several. Organs affected are those involved in the transport or utilization of oxygen (pulmonary, cardiac, blood, vascular function, skeletal muscle oxidative capacity) but are impaired due to cancer treatment and its side effects. Different evidence is available for different organs and their therapy-associated impairments[71, 106, 107]. A distinction can be made between direct and indirect consequences of the therapy. Direct consequences of therapy are, for example, radiotherapy, systematic therapies (e.g. chemotherapy) or supportive therapy (e.g. dexamethasone). Indirect consequences could be categorized into modifiable risk factors (such as reduced muscle mass, general deconditioning) or non-modifiable risk factors (e.g. age, genetics)[105]. In the context of CRF assessment, it is also crucial to consider cardiotoxic agents (e.g., anthracyclines: doxorubicin; high-dose cyclophosphamide), which have a decisive influence on cardiac health and ultimately on risk and outcome in allo-HCT survivors[108, 109]. Anthracycline-induced cardiac toxicity is considered to be permanently damaging the heart tissue and leads to impaired systolic cardiac function or impaired LVEF or generally limited cardiac output[106, 110, 111]. This process also includes a reduction in convective oxygenation and thus a reduced supply of oxygen to the mitochondria. Among other things, these damaging mechanisms are triggered by the reactive oxygen species (ROS) and the associated induction of apoptosis of myocardial cells. In addition, chemotherapies can limit hemoglobin concentration in the blood, which in turn impairs

oxygen delivery and thus also causes a further reduction in arterial oxygen[106]. At least in healthy individuals, the relationship between hemoglobin-level and better CRF values is well documented[39]. Mechanisms such as these lead to a reduction in physical performance and affect presumably directly the CRF. Furthermore the reduced level of physical activity reinforces low CRF-values[71], possibly also in allo-HCT-candidates.

Few investigations have concentrated on the period after allo-HCT and examined CRF in allo-HCT-survivors[112, 113], and pre allo-HCT data are also very sparse. A recent investigation demonstrated that CPET is feasible and can be safely performed in patients prior to myeoablative allo-HCT. Furthermore, univariate analyses showed that the measured CRF values reveal a significant limitation of the patients and both VO_{2peak} and ventilatory threshold (VT) could be identified as predictors for OS and NRM[102]. Further it could be demonstrated, that patients with reduced CRF prior to allo-HCT also suffer from higher symptom burden during the treatment process, experience worse health-related QoL, and have a higher probability of mortality after treatment[95]. Supporting this approach, effects of physical training on survival of allo-HCT patients can be mapped. These data support the suggestion that patients may benefit from increased exercise capacity[114].

In conclusion, CRF is already reduced in patients prior to allo-HCT, but at the same time higher values are most likely essential for the outcome and the transplantation process. Further investigations supporting these findings are still lacking.

Research questions of Manuscript I

The investigation of the limitations in physical performance, operationalized by CRF in comparison to a healthy reference sample. Which influencing factors of CRF can be identified? Is there a particularly vulnerable pre-treatment patient population that may benefit from physical training?

1.6.2 State of the Art Impairments of muscle strength: What's the risk?

In general, a high level of evidence recommends maintenance and improvement of muscle strength or muscle mass for cancer patients both after and during treatment[8]. Simultaneously, it is well known that both cancer treatment and its side effects, can lead to pronounced muscle atrophy.

Physical exercise and targeted training have the potential to increase muscle mass and strength while maintaining or improving physical functioning[115]. Loss of skeletal muscle, which would normally take decades, can occur within months in cancer[116, 117]. This loss is multifactorial and is associated with different clinical consequences. Again, patients can be expected to experience a downward spiral of muscle atrophy and low physical activity. In addition to physical and functional limitations, the consequences of decreased muscles mass include a lower QoL, reduced tolerance of cancer-therapy and worsened prognosis[116, 118]. The expression of muscle loss is thought to be influenced by tumor- and treatment-related factors and subsequent changes in muscle protein turnover, systemic inflammation, mitochondrial dysfunction, and oxidative stress, but lifestyle- or age-related variables are also possible. Many of the underlying molecular biological and cellular processes have not been definitively elucidated[116, 118, 119]. This is partly because the field of research and the pathophysiology are very complex.

The authors Christensen et al. summarize the reasons for muscular dysfunction in cancer patients. Besides malnutrition and physical inactivity (see chapter above), *age and comorbidities* are potential influencing variables. Since oncological diseases increase with age and at the same time muscle mass decreases with age, it is obvious that there is an age-related loss of muscle mass. Furthermore, the quality of muscle decreases with age and a loss of type II muscle fibers can be primarily manifested. In addition, the likelihood and number of comorbidities increases, which can contribute to the aging process through chronically higher inflammation, impaired metabolism and further deconditioning[119].

Tumor-specific effects such as inflammatory processes or altered metabolism were investigated in various preclinical models in muscle. It could be shown that proinflammatory cytokines (TNF-α, IL1-β and IFN-γ9) are released from the tumor depending on the tumor load and thus trigger a profound systematic inflammation. This process activates loss of muscle tissue or protein catabolism. Processes of this type have been demonstrated in cancer patients in muscle biopsies. The results also show that muscle tissue breakdown starts at a very early stage of the disease, before weight loss occurs and is reflected in it. This is compounded by impaired metabolic mechanisms, with tumors competing with other glucose-dependent tissues for energy availability due to the high demand rate of glycolysis[119]. These findings are also supported in a recent review-paper.

Catabolic mechanisms are further determined and thus mitochondrial dysfunction also appears to affect muscle loss. Reduced mitochondrial biogenesis and generation of excess ROS are identified as possible causes[116].

In conclusion, the findings suggest that cancer alone can initiate catabolic mechanisms. This is primarily triggered by increased markers of protein degradation in the ubiquitin-proteasome system (UPS), decreased muscle protein synthesis and metabolic dysfunction[116, 118, 120].

In addition to cancer-associated influence on skeletal muscle loss, *cancer treatments* including chemotherapies, radiotherapy or other agents such as glucocorticoids are also considered responsible. In general, it should be noted that different treatments may also have different effects (e.g. on muscle function or morphology) and may reinforce each other, e.g., through combined irradiation. This makes direct delineation and impact of treatment effects on muscle loss difficult[116]. For example, there is a reduction in muscle mass caused by increased protein catabolism and decreased protein synthesis. Glucocorticoids (group of corticosteroids), for example, have a catabolic effect on skeletal muscle in the context of immunosuppression after transplantation[121], while amino-acid efflux simultaneously reduces the rate of protein synthesis[122]. Anthracycline-containing treatments (e.g. in patients with ALL) can also cause skeletal muscle impairments, such as abnormalities in mitochondrial respiratory or increased ROS, respectively oxidative stress[123, 124].

Some studies have looked more closely at this type of treatment and describe the negative effects on the muscles (including muscle weakness)[125-127], but also on other physiological areas (e.g. bone density)[127]. Corticosteroid administration probably has a dose-dependent relationship with muscle atrophy and primarily affects glycolytic fast-twitch muscle fibers type II[128].

Of particular note is the group of glucocorticoids, because they are used in the standard treatment of hematopoietic malignancies of lymphoid diseases like ALL, CLL, MM, HL and NHL. For example, dexamethasone (DEX) is routinely included in all chemotherapy protocols to induce cell apoptosis[129].

These negative effects can also be described and mapped in the context of allo-HCT. Thus, it could be demonstrated that the total corticosteroid dose correlated with a decrease in handgrip and knee extension strength ($P<0.01$). In addition, treatment probably has a negative effect on other areas of physical functioning[130].

Several studies investigated the muscle strength status in hematologic patients, also in allo-HCT candidates. A retrospective study reveals significant respiratory- and skeletal muscle

weakness in patients after treatment by allo-HCT[131]. These data are supported and show these limitations even before allo-HCT[132]. In a longitudinal designed study with lymphoma patients, it was also proven that the strength ability (quadriceps muscle force) is already reduced before the treatment and additionally decreases in the further course of treatment[133]. Another retrospective study found reduced knee extensor muscle strength in patients undergoing allo-HCT and observed that these low values before allo-HCT could predict OS and NRM after transplantation[134].

Against the background of a frequently occurring sarcopenia, a close association with muscle strength can be suspected. It was identified that patients have reduced muscle strength even before allo-HCT, and this limitation is often associated with sarcopenia[135]. This is interesting because sarcopenia seems to affect outcomes of cancer patients[136, 137] and seems to be associated with worse OS and higher NRM after allo-HCT[138]. This is corroborated by the fact that in allo-HCT candidates, risk stratification can be performed from a combined assessment in terms of muscle mass, muscle strength and the determination of VO_{2peak}. For here, too, all-cause mortality and mortality without recurrence were increased threefold in the sarcopenic group[96]. Supporting data for these analyses identify low pretransplant BMI, underweight, obesity[139] or pretransplant weight loss in MDS-patients as a risk factor of poor survival[140]. It is clear that muscle mass and muscle strength play an important role in the risk assessment of allo-HCT candidates and although further studies exist in this area, a systematic review and meta-analysis concluded that research is still needed to balance the risks and benefits of allo-HCT as early as possible[141].

Research question of Manuscript II
Description of limitations in physical performance operationalized by muscle strength and compared to a healthy reference population. Which influencing factors of muscle strength can be identified? Is there a particularly vulnerable pre-treatment patient population that may benefit from physical training?

1.6.3 State of the Art Pretraining

As has been shown, the physical performance parameters "CRF" and "muscle strength" of allo-HCT candidates are significantly reduced directly prior the treatment process of allo-HCT. These results are thus in line with the current state of research. Due to their prognostic relevance in the context of the risk stratification, it is important that patients undergo this procedure as "fit" as possible. Exercise training offers a substantiated and promising impact to achieve this goal.

For various types of cancer and cancer patients, it is now known that exercise training has numerous beneficial effects on physical performance (endurance capacity and muscle strength), psychological factors or fatigue at different phases of the therapy, resulting in enhanced QoL. Exercise training is generally considered safe, evidence-based and represents a well-established method to specifically improve muscle strength and CRF[2, 142-144], also in hematological patients[145]. These various beneficial effects are also known for patients with hematological malignancies and also specifically for patients treated with allo-HCT. Therefore exercise effects have been demonstrated e.g. on endurance capacity, muscle strength, QoL or fatigue[146-148]. Furthermore, exercise programs may have a cardioprotective and protective effect on the muscular, leading to a better health outcome and reduced complication rate in allo-HCT candidates[145]. However, most of these existing exercise interventions were performed during and/or after the treatment.

Pretraining exercise therapy for cancer patients is a comparatively new field of research. For example, several investigations in different cancer subtypes show improvements from pretraining interventions prior to treatment[149], yet pretraining-interventions are still sparse. Especially in hematologic diseases there is a considerable lack for the time prior to allo-HCT.

One feasibility study with hematological patients conducted a pre-transplantation exercise program (endurance, muscle strength and relaxation exercises) in the waiting period for allogeneic or autologous transplantation. They demonstrated positive trends in physical function, QoL and fatigue and conclude: exercise training prior transplantation is safe and feasible. Although partly comparable processes exist in the preparation of the different treatment, these results are heavily limited because the intervention group consisted only of autologous transplant patients[150]. But, another nonrandomized study reported significant improvements in CRF with a home-based interval exercise training to prepare patients to allo-HCT. Results in autologous patients and in the Six-Minute-Walk Distance (6MWD) were not significant, but they show positive trends[151]. Based thereon, a pilot-RCT, designed for allo-HCT-candidates tested the effect of a 5-12 week home-based pretraining interval exercise training program on CRF. But no significant differences between the groups could be demonstrated. It is unclear in this regard why better effects were generated in the context of the previous investigation. A reliable evaluation is difficult due to the final small number of cases[152]. It remains unclear how a pretraining approach can be implemented in patients prior to allo-HCT. However, the authors point out that the aim “get fit for allo-HCT” should be further pursued[152, 153].

Nevertheless, supporting this approach, effects of physical training on survival of allo-HCT patients can be achieved. These retrospective data reinforce the suggestion that patients may benefit from increased exercise capacity[114]. Due to the limited time frame before allo-HCT

and the simultaneous efficacy, high-intensity training programs might be recommended. First data from a meta-analysis seem to support this suspicion and demonstrate effects of a training program prior to cancer treatment on CRF and health-related outcomes[154].

Research question of Manuscript III

Is a high intensity training (HIIT and RT) of allo-HCT candidates safe, feasible and efficient shortly prior transplantation to improve physical performance?

2 METHODS

The manuscripts of the present cumulative dissertation are based on the data of two studies. Firstly, the PETRA study (ClinicalTrials.gov identifier: NCT01374399) and secondly the PRESENT-P pilot study (Clinical Trials.gov identifier: NCT03080792). Both studies were conducted at the University Hospital Heidelberg/ the National Centre for Tumor Diseases (NCT) in Heidelberg (Germany).

The following subchapters briefly report on: participants, interventions and assessments. Since both studies examine cardiorespiratory fitness as well as muscle strength, the main-assessment methods are described in more detail in the joint Chapter 2.3.

2.1 PETRA STUDY

As already described in Chapter 1.3, allo-HCT is the only method with curative prospects for many blood cancers, especially when, for example, conventional chemotherapeutic treatment approaches fail. The further development of the treatment procedure in recent years has led to an increase in successfully performed transplantations, expanded the patient field to include older patients and has been able to reduce therapy-associated mortality. Against this background, the importance of effective measures that support the reconstitution process of patients in the acute and rehabilitation phase comes to the fore. In the course of treatment, numerous biopsychosocial problems arise that need to be managed, such as cancer-related fatigue syndrome, symptoms of depression or anxiety, inadequate physical performance, and changes at the endocrinological and hematological levels. The PETRA study investigates to what extent these complications can be influenced by physical training and whether this can also affect the prognosis after transplantation. It is a two-armed study with a randomized ("biased-coin"-method) intervention (physical training) and control group (Progressive Muscle Relaxation *PMR* according to Jacobson).

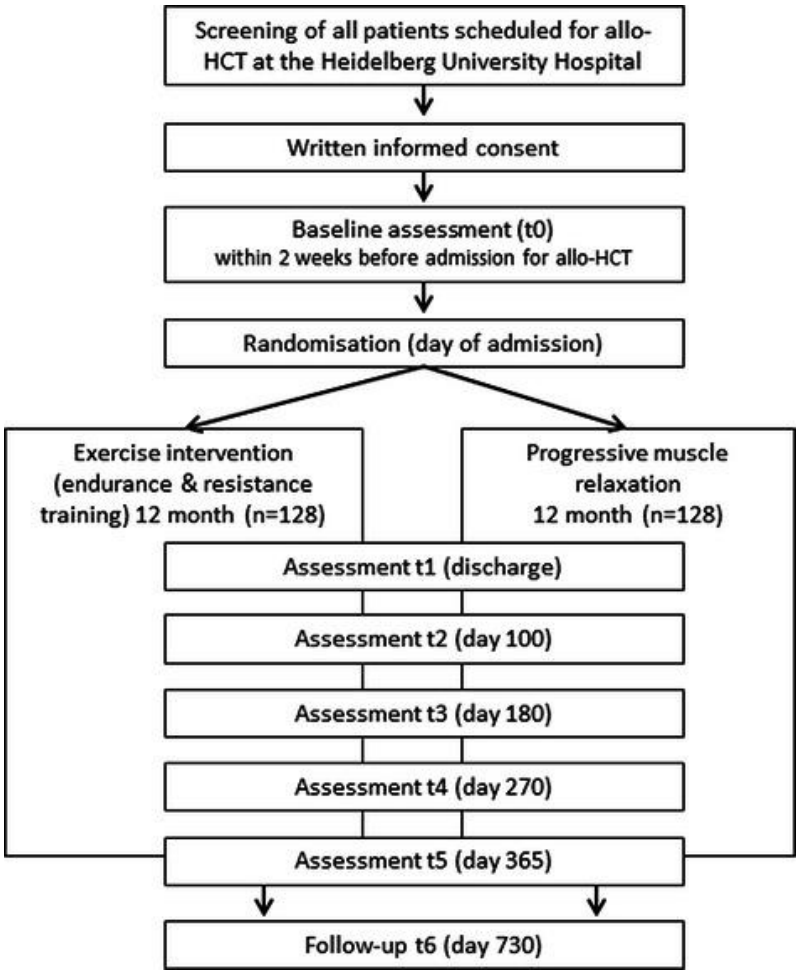

Figure 2. Study Flow of the PETRA study[1]

PARTICIPANTS

All Hematological patients, planned for allo-HCT at University Hospital Heidelberg or at another cooperation site, were eligible for the PETRA study. Exclusion criteria are listed in clinicaltrials.gov. During their preliminary examination, the patients were informed about the study by the treating physician of the respective center and received an information sheet. After some time, they were contacted by the study center to clarify any open questions. For better planning of the sports motor diagnostics, the patients were asked on this occasion about a non-binding vote for study participation. The consent form itself was then signed after renewed clarification on the day of the baseline diagnostics.

INTERVENTIONS

The patients of the intervention group performed training combining strength and endurance. Basically, exercises were built up during the inpatient phase, which could then be continued later in the home environment and/or in a training center close to the patient's

home. Relevant training centers were trained by study personnel beforehand and were contacted regularly to guide and support the patients during training. After discharge, patients were followed up via telephone, internet (e-training) if necessary, and regular meetings at the transplant center.

ASSESSMENTS

	testing time	duration	contents
T0	outpatient pre-test	~2.5 hrs	sport motor tests and questionnaires
T1	on or one day before discharge	~1 hr	
T2	~100 days pre transplantation	~1 hr	
T3	~180 days pre transplantation	~2.5 hrs	
T4	~270 days pre transplantation	~1 hr	
T5	~365 days pre transplantation	~2.5 hrs	
T6	~730 days pre transplantation	~2.5 hrs	

Figure 3. Assessments PETRA study

Sport motor tests

Endurance performance diagnostics (spiroergometry via CPET on an electronically braked cycle ergometer (Ergoselect 100; Ergoline, Bitz, Germany), only T0, T3, T5 and T6 due to the higher time expenditure)

Spiroergometric performance tests are part of standard medical diagnostics. As part of the study, diagnostics are carried out according to the (slightly modified) WHO standard protocol (multiple stage testing; 2 minutes of exercise per stage). Generally, performance is increased by 25 watts per stage. The entry level is 50 watts.

Endurance performance diagnostics (6-Minute-Walk Distance Test test, all measurement times)[155, 156]

The 6-minute walk test (6MWT) is a very practical test for determining a patient's endurance capacity. During the testing time of 6 minutes, the person being tested is instructed to walk as many meters as possible. The 6MWT is an internationally recognized test for determining the endurance capacity of patients with various chronic illnesses.

Isokinetic/ isometric muscle diagnostics via IsoMed 2000-System® D&R Ferstl GmbH, Hemau, Germany (only T0, T3, T5 and T6 for reasons of time economy and feasibility) and handheld dynamometry (all measurement times)

As part of the study, the large muscle groups of the extremities (leg flexors/extensors and arm flexors/extensors) are examined.

For a more detailed description, see Chapter 2.3.

Questionnaire diagnostics

EORTC-QOL-C30 (European Organization for Research and Treatment of Cancer – Quality of Life)[157] *incl. HDC-29 Modul*[158]

The EORTC-QOL-C30 questionnaire is a specific instrument for measuring quality of life in cancer patients. The extended HDC-29 module is specially tailored to the situation of patients after high-dose chemotherapy and HSCT.

MFI (Multidimensional Fatigue Inventory)[159]

The MFI is a questionnaire with 20 items measuring the severity of fatigue. The items are assigned to five different scales, which differentiate between "general fatigue", "physical fatigue", "reduced activity", "reduced motivation" and "mental fatigue".

NCCN Stress- (Distress-) Thermometer[160, 161]

The Distress Thermometer is a screening instrument developed by the National Comprehensive Cancer Network (NCCN) in the USA to record the type and extent of existing stress in oncology patients.

Depression Score (Allgemeine Depressionsskala - ADS)[162]

The general depression scale by Hautzinger and Bailer is a self-assessment instrument that asks about the presence and duration of impairment due to depressive affects, physical complaints, motor inhibition and negative thought patterns. The long form with 20 items was used in the study.

Questionnaire for the assessment of control beliefs about illness and health (Fragebogen zur Erfassung der Kontrollüberzeugung zu Krankheit und Gesundheit – KKG)[163]

The KKG is an instrument developed by Lohaus & Schmitt to assess the belief in control over illness and health. It comprises a total of 21 items, which can be summarized into 3 subscales (internality, social externality and fatalistic externality) of 7 items each. The KKG is based on Rotter's social learning theory.

Data from the present manuscripts were collected at testing time T0. Retrospectively, data were collected for the time before allo-HCT and were obtained from the patient documentation system and the physician's letters.

2.2 PRESENT-P STUDY

As the previous chapters showed, exercise is generally recommended for cancer patients. Because there is evidence of physical performance before allo-HCT as a predictor of OS but no investigational studies, the Present-P study was designed. Its goal is to focus on:

- *the feasibility and safety of high-intensity endurance training and resistance training (RT) prior allo-HCT, the estimation of the number of eligible patients, the evaluation of the recruitment procedures and reasons for non-participation*
- *the effect of exercise prior allo-HCT*

The study was planned with n=30 hematologic patients. The intervention period was 4-8 weeks before allo-HCT until admission. Assessments took place prior intervention (T0, baseline) and post intervention (T1, 4-12 weeks later)/prior admission for allo-HCT. The study was conducted at the University Hospital Heidelberg and other collaborating sites (Freiburg, Cologne, Dresden and Frankfurt).

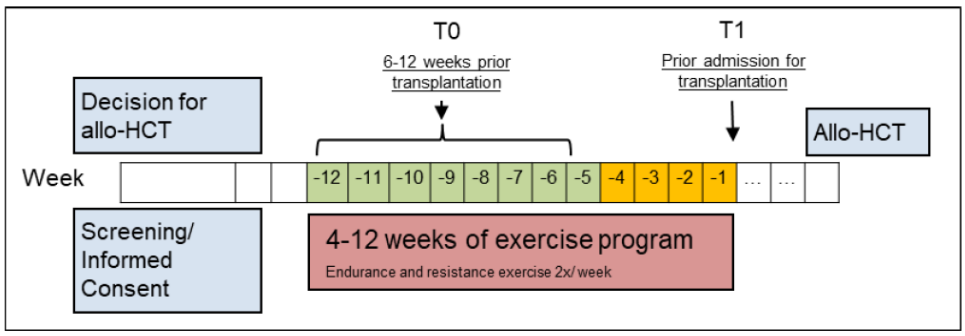

Figure 4. Study scheme of the PRESENT-P study (Study protocol PRESENT-P)

PARTICIPANTS

Hematological patients who were 18 years of age or older and were planned for allo-HCT at University Hospital Heidelberg or at another cooperation site, were eligible for the PRESENT-P study. The detailed inclusion and exclusion criteria are listed in clinicaltrials.gov. Patients were briefly informed about the possibility of participating in the study by their treating physicians. Interested patients were then informed in detail by study staff. Patients were contacted either at a preparatory visit (5-6 weeks prior admission for allo-HCT) or at an earlier stage during chemotherapy treatment. Those patients who agreed to participate in the trial and provided written informed consent were enrolled in the study.

INTERVENTIONS

The total length of the intervention period (4-12 weeks), starting at least 4 weeks prior admission, depended on the final planning of the transplantation. Due to the short period of the intervention, it was decided on a high-intensity exercise program: 30min high intensity interval exercise training (HIIT: repeated bouts of high-intensity exercise interrupted with recovery periods) on a bicycle ergometer followed by 30min high-intensity RT twice a week.

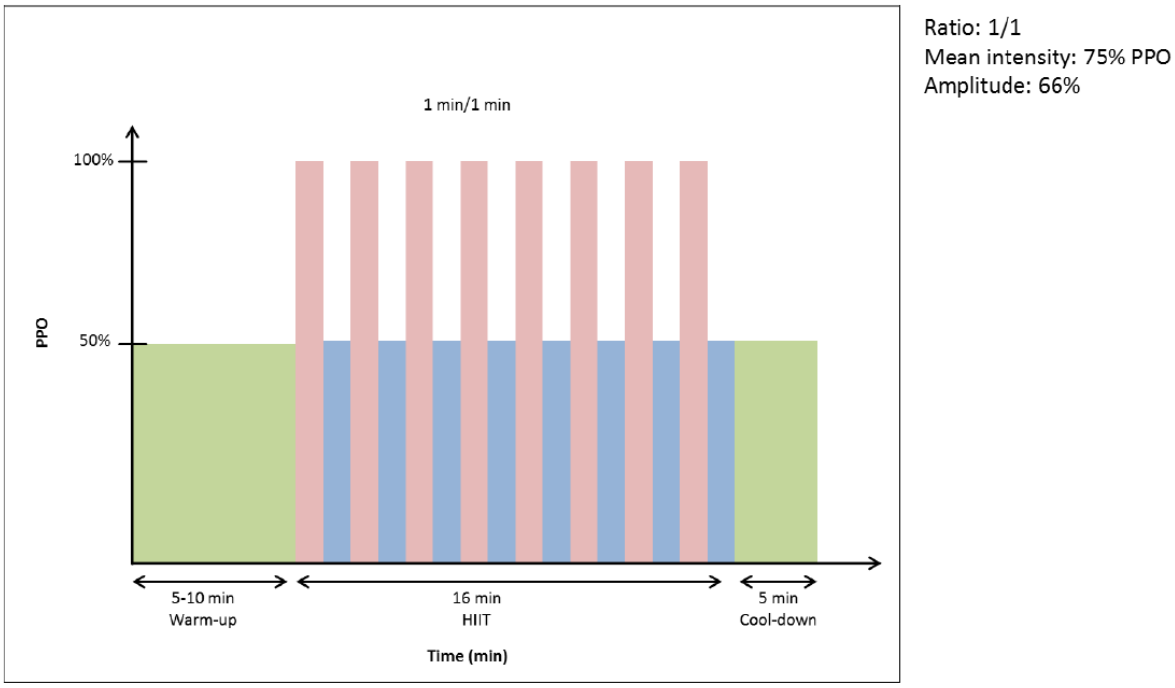

Figure 5. HIIT Protocol (Study protocol PRESENT-P)

HIIT: After the warm-up phase, patients performed 8 times a 1-min high-intensity bout at 90%-100% peak power output (PPO, achieved in the CPET) intensity, interrupted by 1min rest periods at 50% PPO intensity.

RT: The resistance training included 4-6 exercises, targeting the whole body (legs, arms, shoulders, back, and chest). Resistance training machines were used as well as free weights. The patients performed two sets of repetitions with a maximum of 12 repetitions. The sets were interrupted by a resting time of 1 minute.

For both exercise trainings HIIT and RT, the following applied: 1. High intensity training was applied only in the last 4 weeks. In the 4 weeks prior (0-4 weeks), the patients went through a familiarization period, exercising at a slightly lower level of exercise intensity. 2. The intensity of the training was based on the individual results of the CPET and the one repetition maximum test (1RM test) prior intervention. 3. During hospitalization, the exercise protocol was modified and the intensity reduced accordingly to the individual thrombocytes. 4. In general, when patients were not able to exercise at the high intensity, it was reduced to a tolerable intensity.

ASSESSMENTS

The participants had two study visits (T0 and T1) which took about 2h each. The baseline assessment (T0) took place 5-12 weeks before admission for allo-HCT. The final visit took

place at the day of admission for allo-HCT (T1). Both measurement times included the same endpoint assessments, such as:

Feasibility parameters:
Adherence to the exercise interventions (documentation)
Recruitment procedure (evaluation recruitment and reasons for non-participation)
Safety (documentation)

Exercise performance tests and physical function:
Cardiorespiratory fitness (VO_{2peak} ; CPET including ECG, 6 minute walk test)[164-167]
Strength performance (isometric and isokinetic, one-repetition maximum, hand-grip)[164, 168, 169]

Body composition
BMI, Body Impedance Analyze (BIA)[170, 171]

Patient-reported outcomes (PROs):
Quality of life (EORTC QLQ-C30[157] and HDC-29[158])[172], overall, functions and symptoms
Fatigue (MFI 20)[159]
Depression score (ADS, German version of CES-D)[173]

2.3 THE MAIN ASSESSMENTS OF CARDIORESPIRATORY FITNESS AND MUSCLE STRENGTH

This chapter presents the main measurements of the PETRA study and the PRESENT-P study that describe the physical performance, CRF and muscle strength. The more detailed description of the assessment protocols and procedures is based on the manuscripts.

The cardiopulmonary exercise test (CPET) is considered the gold standard method[174] for the assessment of physical performance. Physiological parameters are related to the underlying metabolic system, which at the same time provides highly reproducible information[175, 176]. Among other parameters, the VO_{2max} is measured, which represents the CRF.

In general, VO_{2peak} is preferred over VO_{2max} as terminology in the present context, as the required plateau ("leveling") of VO_{2max} is often not achieved. This is compliant for clinical questions[174, 175]. The VO_{2peak} indicates the amount of oxygen that can be taken in during exercise. It can be considered a "brutto criterion" of cardio-pulmonary-metabolic capacity because it includes all power-generating and -processing mechanisms. Involved are external respiration, gas exchange in the lungs, cardiac output, O_2 transport in the blood, load-appropriate distribution of cardiac output, and O_2 uptake into working muscles. It is described by Fick's principle, which maps the arteriovenous oxygen difference [175, 177]. VO_{2peak}

is expressed absolutely in ml/min or normalized to body weight for better comparability in ml/kg/min and there are standard values [176]. In the present manuscript, the expected individual VO_{2peak} values were calculated according to Koch et al. for healthy individuals taking into account age, gender, and BMI distribution and were used as a reference because they contain the comprehensive European person characteristics[178].

In conclusion, an assessment of integrative physiological subdomains is possible, which in summary not only reflects maximal exercise capacity but also provides information about ability to perform activities of daily living[179]. Moreover, determination of VO_{2peak} has profound diagnostic and prognostic value, not only in cardiovascular or pulmonary diseases[180]. CPET is also used in various scientific and clinical questions in oncological patients[101, 165, 181, 182], including hematological patients or allo-HCT-candidates[95, 102, 183] (see Chapter 1.6.1).

ASSESSING CARDIORESPIRATORY FITNESS IN THE PETRA AND PRESENT-P STUDY

To assess baseline CRF of the participants, a CPET was performed prior admission. The CPET was conducted on an electronically braked bicycle ergometer (ergoselect 100, Bitz, Germany and Corival, Lode B.V. Medical Technology, Groningen, Nederland). Gas exchange was measured using a breath by breath system (Ergostik, Geratherm Respiratory, Bad Kissingen, Germany), which was calibrated according to the instructions of the manufacturer before each test. In the PETRA study, a stepwise incremental protocol was applied, which started at 50 Watt (W). The work rate was increased every 2 min by 25 W until voluntary exhaustion or occurrence of medical reasons. Cadence was kept constant between 60 and 70 repetitions per minute (rpm). A 12-lead electrocardiogram continuously monitored and blood pressure was measured every 2 min during the test. In the context of the PRESENT-P study the CEPT started with a 2-min unloaded warm-up phase. The load was increased by 10 W every minute, starting at 20 W[164]. For analysis, we determined VO_{2peak} and the VO_{2peak} in relation to body weight (ml/min/kg) referring to the American Thoracic Society/ American College of Chest Physicians (ATS/ACCP) recommendations [174]. For VO_{2peak} and heart rate, the highest 30s average value during or immediately after termination of CPET was considered. We used the following criteria to determine patients exhaustion: respiratory exchange ratio (RER) >1.1 or HR >85% of age predicted maximum.

ASSESSING MUSCLE STRENGTH IN THE PETRA AND PRESENT-P STUDY

To measure isometric muscle strength, the IsoMed 2000-system B-series version (D&R Ferstl GmbH, Hemau, Germany) was used in the PETRA and the PRESENT-P study. Several

studies now exist that have been able to make substantiated statements about the reliability and validity of this measurement[169, 184, 185]. Isometric and isokinetic assessments were chosen because it is considered the gold-standard method for determining muscle strength [119, 164] and has been successfully used in various cancer populations[186-189]. Our test protocol includes the assessment of the maximal voluntary isometric contraction (MVIC) and the maximal isokinetic peak torque (MIPT) of the representative muscle group (knee extension) of the lower extremities and hip muscles (hip flexion). The measured values are reported as Newton metre (Nm).

It was ensured, that the axis of rotation through the knee and hip always formed an angle of 60 degrees (where 0 degrees is a straight limb). In order to obtain direct feedback, the monitor displaying the force curve was positioned so that both the subject and the instructor had it in view at all times. The subject was repeatedly verbally encouraged to generate the highest possible force during the test. Each deceleration resulted in a torque artifact, which often exceeded the actual peak torque. These artifacts were removed using a filter so that only gravity corrected data was later used for analysis. To ensure that the measured values were not distorted by extraneous movements, the subjects were additionally secured with straps, attached at thigh, pelvic and torso. In addition, handlebars were used on both sides to restrain the subjects during the test.

Assessment of MVIC

MVIC was tested bilaterally for knee extensor (angle position 36°) and hip flexor (angle positon 33°). These were consistently the strongest angular positions. The subjects were instructed to push with their maximum force against an insurmountable resistance in the respective position (knee extensors and hip flexion). Contraction time was limited to 6s for each position.

Assessment of MIPT

MIPT was tested bilaterally for extensors and flexors of the knee and hip. For isokinetic measurements, the range of motion ranged from 10° to 90° flexion in the knee (straight leg is 0°) and from 10° to 100° in the hip (straight leg in supine position is 0°). The subject was instructed to move the lever arm as firmly and as far as possible while alternating between extension and flexion at a constant angular velocity (60°/s). Up to 10 times this movement could be performed, and the highest torque value of all cycles on the joint side in question was analyzed.

3 MANUSCRIPT I

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Authorship contributions (categories based on the recommendations of Supportive Care in Cancer):
Conception and design: Joachim Wiskemann, Martin Bohus
Provision of study materials or patients: Joachim Wiskemann, Rea Kühl, Matthias Limbach, Peter Dreger, Birgit Friedmann-Bette, Friederike Rosenberger, Thomas Luft, Andrea Bondong
Collection and assembly of data: Rea Kühl, Matthias Limbach
Statistical analyses and interpretation of the data: Joachim Wiskemann, Matthias Limbach, Nikolaus Kleindienst, Friederike Rosenberger, Rea Kühl
Drafted and finalized the manuscript: All authors

Influencing factors of cardiorespiratory fitness in allogeneic stem cell transplant candidates prior to transplantation

Matthias Limbach[1] & Rea Kuehl[1] & Peter Dreger[2] & Thomas Luft[2] & Friederike Rosenberger[1] & Nikolaus Kleindienst[3] & Birgit Friedmann-Bette[4] & Andrea Bondong[2] & Martin Bohus[3] & Joachim Wiskemann[1]

[1]Department of Medical Oncology, National Center for Tumor Diseases (NCT), Heidelberg University Hospital, Im Neuenheimer Feld 460, 69120, Heidelberg, Germany
[2]Department of Medicine V, Heidelberg University Hospital, Heidelberg, Germany
[3]Central Institute of Mental Health, Mannheim, Germany
[4]Internal Medicine VII (Sports Medicine), Heidelberg University Hospital, Heidelberg, Germany

Abstract

Purpose Cardiorespiratory fitness (CRF) seems to be prognostic prior to allogeneic stem cell transplantation (allo-HSCT). Influencing factors of CRF in allo-HSCT candidates have not been studied so far. Aim was to identify potentially influencing factors on CRF.
Methods To assess CRF, a maximal cardiopulmonary exercise test (CPET) was performed on average 2.6 ± 7.2 days prior to admission. A regression analysis was conducted, with the following predictors: gender, age, body mass index (BMI), time between last therapy and allo-HSCT (t_Therapies), number of cardiotoxic therapies (n_Cardiotox), number of transplantations (n_Transplantations), comorbidity index (HCT-CI), hemoglobin level of the last 3 months (area under the curve), and physical activity.
Results A total of 194 patients performed a CPET. VO_{2peak} was significantly reduced compared with reference data. In total, VO_{2peak} was 21.4 ml/min/kg (− 27.5%, $p < 0.05$). Men showed a significant larger percentage difference from reference value (− 29.1%, $p < 0.05$) than women (− 24.4%). VO_{2peak} was significantly ($p < 0.05$) influenced by age ($\beta = -0.11$), female gender ($\beta = -3.01$), BMI ($\beta = -0.44$), n_Cardiotox ($\beta = -0.73$), hemoglobin level ($\beta = 0.56$), and physical activity prior to diagnosis ($\beta = 0.10$).
Conclusions Our study demonstrates a decreased CRF indicating the potential need of prehabilitative exercise. We revealed some influencing factors on CRF. Those patients could benefit the most from exercise.
Keywords: Exercise; Leukemia; Lymphoma; Oncology; Risk management.

Introduction

The number of performed allogeneic hematopoietic stem cell transplantations (allo-HSCT) worldwide has increased over the past decades [1]. This development is related to the extended donor availability and improved transplant techniques such as reduced intensity conditioning or a better usage of the immunotherapeutic graft-versus-leukemia effect, as well as enhanced supportive measures [2]. As a consequence, mortality rates of allo-HSCT are decreasing constantly, however, remain on a considerable high level [2]. A recent retrospective cohort study demonstrated a decline for non-relapse mortality from 41 to 26% comparing the years 1993–1997 and 2003–2007 [3]. Therefore, an accurate risk-benefit stratification is still vital for decision-making in allo-HCT candidates.

Several assessment tools are available for calculating individual patient risk and to define suitable candidates for allo-HSCT like the comorbidity index (HCT-CI), the Karnofsky performance status (KPS), or the European Group for Blood and Marrow Transplantation (EBMT) risk score [4,5,6]. Recently, measurements of cardiac and pulmonary function were introduced to determine patients' physical function and possess prognostic information prior to transplantation [7, 8]. It could be demonstrated that decreased cardio respiratory fitness (CRF) values are associated with a lower health-related quality of life, a higher symptom burden, and a higher risk of mortality in patients undergoing HSCT [8]. This has also been shown in other cancer populations [9, 10].

Since CRF could be modified by exercise intervention approaches, there is a certain interest to identify factors explaining lower CRF value prior to HSCT. However, the pre-treatment situation in HSCT patients is quite complex, and it is still uncertain on what affects the physical performance prior to HSCT. Initial approaches emphasized that the amount of prior chemotherapies or months of received chemotherapy prior to HSCT might impact CRF [8], but comprehensive data analyses are still missing. Therefore, we aimed to evaluate CRF and its influencing factors in patients immediately prior to allo-HSCT.

Patients and methods

Setting and patients

We analyzed baseline data from $n = 256$ allo-HSCT patients from the study Physical Exercise Training versus Relaxation in Allogeneic stem cell transplantation (PETRA), a large ongoing two-arm randomized controlled trial (RCT) of exercise intervention. All patients, scheduled for an allo-HSCT at the Heidelberg University Hospital, age ≥ 18 years and able to understand and follow the study protocol were eligible to be enrolled in the PETRA study. Exclusion criteria were inability to walk or stand, unstable bone lesions, severe neurological deficiencies, severe cardiac or cardiovascular diseases, and severe pulmonary global insufficiency. Cross-sectional data were obtained prior to admission for allo-HSCT. The study has been approved by the ethics committees of the Ethics Committee II of the University of Mannheim (number 2009–349 N-MA) and the Ethics Committee of the University of Heidelberg (number S-021/2011), and is registered at ClinicalTrials.gov (NCT01374399). All patients provide written informed consent.

Determination of CRF

To assess baseline CRF of the participants, a cardiopulmonary exercise test (CPET) was performed prior to admission. The CPET was conducted on an electronically braked bicycle ergometer (ergoselect 100, Bitz, Germany and Corival, Lode B.V. Medical Technology, Groningen, Netherlands). Gas exchange was measured using a breath by breath system (Ergostik, Geratherm Respiratory, Bad Kissingen, Germany), which was calibrated according to the instructions of the manufacturer before

each test. A stepwise incremental protocol was applied, which started at 50 W, and work rate was increased every 2 min by 25 W until voluntary exhaustion or occurrence of medical reasons. Cadence was kept constant between 60 and 70 rpm. A 12-lead electrocardiogram continuously monitored and blood pressure was measured every 2 min during the test. For analysis, we determined VO_{2peak} and the VO_{2peak} in relation to body weight (ml/min/kg) referring to the ATS/ACCP recommendations [11]. VO_{2peak} and heart rate were considered the highest 30s average value during or immediately post-termination CPET. We used the following criteria to determine patients' exhaustion: respiratory exchange ratio (RER) > 1.1 or HR > 85% of age predicted maximum.

Potentially influencing factors for CRF

Additionally, we investigated potentially influencing factors for CRF. Patients were asked to self-report the level of physical activity (walking, cycling, and other sports) in a typical week in the year before diagnosis with a proved questionnaire [12]. The degree of physical activity was operationalized with metabolic equivalent of task (MET). MET hours per week (MET × h/week) were calculated by summing the average hours per week spent in walking, cycling, or other sports. The following clinical data prior to allo-HSCT were extracted from the medical records as potentially influencing factors: number of cardiotoxic therapies (n_Cardiotox), number of transplantations (allogeneic and autologous, n_Transplantations), months between last therapy to allo-HSCT (t_Therapies), KPS, remission status, the hematopoietic cell transplantation-specific comorbidity index (HCT-CI), primary hematological malignancies, LVEF (left ventricular ejection fraction), hemoglobin levels, age, gender, and body mass index (BMI). BMI was calculated as body weight divided by square of height in meters. Hemoglobin (g/dl) level was measured on the day of CPET assessment. Further, we calculated area under the curve values for hemoglobin levels over the last 3 months prior to allo-HSCT (Hemoglobin_auc). The HCT-CI was determined according to guidelines and separated into low to intermediate risk group (< 3) and high risk group (≥ 3) [13].

Statistical analyses

Baseline clinical and demographic data were reported by descriptive analysis and are reported as mean ± SD and range. Differences between measured values of VO_{2peak} and reference values were reported as percent differences. The observed values were compared with reference values by using paired sample *t* test. Expected individual VO_{2peak} values were calculated by Koch [14] for healthy people of considering age, gender, and BMI distribution. Hemoglobin level over the last 3 months was calculated as area under the curve score using the trapezoidal rule [15]. To identify determinants of CRF prior to allo-HSCT, a multivariate regression analysis was conducted. The following independent variables were entered into the regression model simultaneously: age, gender, BMI, n_Transplantations, n_Cardiotox, t_Therapies, HCT-CI, Hemoglobin_auc, and physical activity. We chose VO_{2peak} as representative value for CRF and therefore as the dependent variable. In the second regression model, the deviation VO_{2peak} from healthy reference was used as the dependent variable. The level of statistical significance was set at $p < 0.05$. Data were analyzed using IBM SPSS v. 22.

Results

Five hundred forty-four patients were screened and $n = 99$ were ineligible due to exclusion criteria (18.2%). From $n = 445$ (81.8%) eligible patients, $n = 178$ (40%) did not participate. Reasons were $n = 94$ (52.8%) not interested, $n = 39$ (21.9%) due to organizational problems (postponement, no exercise testing capacity available due short notice admission to allo-HSCT), and $n = 45$ (25.3%) because of other reasons. Two hundred sixty-seven patients were included of whom $n = 200$ participated in CPET. Major reasons for not being able to perform CPET were infections $n = 27$ (10.1%), insufficient blood values $n = 7$ (2.6%), and other medical reasons $n = 13$ (4.9%). Twenty patients (7.5%) did not participate due to unexpected early inpatient admission or unpredictable date collision. Five of $n = 200$ VO_{2peak} values were not analyzable. One patient did not tolerate the face mask (Fig. 1). No serious adverse events occurred.

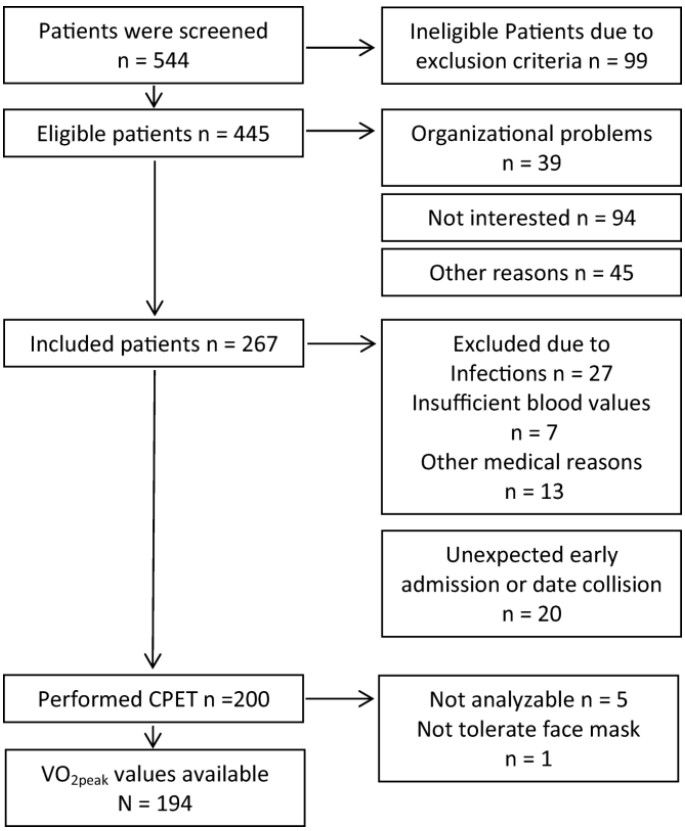

Fig. 1 Patient flow chart showing the numbers of patients who were available for cardiopulmonary exercise test (CPET)

Clinical data and demographics of study participants who performed CPET are described in Table 1. Patients had a mean age of 54.1 ± 11.5 years. Main diagnosis was acute leukemia (AML, 29.9%). They were on average 36.6 ± 47.5 months after main diagnosis. Mean hemoglobin at the day of CPET testing was 11.7 ± 1.8 (g/dl) and hemoglobin level during the last 3 months (Hemoglobin_auc) was 11.4 ± 1.9 (g/dl). On average, the patients performed the CPET 2.6 ± 7.2 days prior to admission. There is a significant association between n_Transplantations and n_Cardiotox ($r = 0.502$, $p = <0.001$). The

analysis of number of transplantations in the patients history showed that n = 47 (24.2%) patients received one or more previous transplantations.

Table 1 Baseline descriptive data

	n	Mean	SD	Range
Age (yr) at diagnosis	194	54.1	11.5	18-75
Gender, n (%)	194 (100)	-	-	-
Males	130 (67)			
Females	64 (33)			
BMI (kg/m²)	192	26.5	5.1	17-57
Diagnosis, n (%)	194 (100)	-	-	-
AML	58 (29.9)			
ALL	10 (5.2)			
CLL	39 (20.3)			
MM	19 (9.8)			
CML/MPS	17 (8.7)			
MDS	16 (8.2)			
other Lymphoma	32 (16.3)			
other	3 (1.6)			
Time from diagnosis to alloHSCT (month)	194	36.6	47.5	0-328
Time between exercise test to admission alloHSCT (days)	194	2.6	7.2	0-47
HCT-CI (n)	184	0.9	1.5	0-8
<3	158			
≥3	26			
Missing	10			
KPS (n)	190	92.7	6.5	100-70
<90	19			
≥90	171			
Missing	4			
Hemoglobin day of CPET testing (g/dl)	194	11.7	1.8	6.8-17.0
LVEF (n)	181	-	-	-
>55%	163			
45-54%	14			
30-44%	4			
<30%	0			
Missing	13			
Remission status prior alloHCT (n)	193	-	-	-
CR	70			
PR	73			
No CR	46			
Unknown	4			
Missing	1			
MET (h/week)	194	7.6	14.9	0-99.5
Smokers (n)	185			
Current	8			
Ever	62			

Year before diagnosis	27			
Never	88			
Missing	7			
VO2peak_rel (ml/kg/min)	194	21.4	5.7	8-41
VO2peak (l/min)	194	1.71	0.5	0.7-3.4
Time since last therapy (month)	194	2.3	4.4	0-54
Hemoglobin last 3 month (g/dl)	192	11.4	1.9	6.5-15.7
Missing	2			
Amount of cardio toxic agents	194	1.5	1.4	0-9
Number of previous transplantations	194	0.3	0.6	0-3

N, number of patients; *BMI*, body mass index; *HCT-CI*, comorbidity index by Sorror; *KPS*, Karnofsky performance status; *LVEF*, left ventricular ejection fraction; *allo-HCT*, allogeneic stem cell transplantation; *CR*, complete remission; *PR*, partial remission; *AML*, acute myeloid leukemia; *ALL*, acute lymphocytic leukemia; *MM*, multiple myeloma; *CML*, chronic myeloid leukemia; *MPS*, myeloproliferative syndrome; *MDS*, myelodysplastic syndrome; *MET*, metabolic equivalent of task

CRF in relation to normal values

VO2peak values were available in 194 patients. All descriptive data of predictors and VO2peak are depicted in Table 1. Figure 2 shows the deviation of measured VO2peak values and the healthy reference values of CRF.

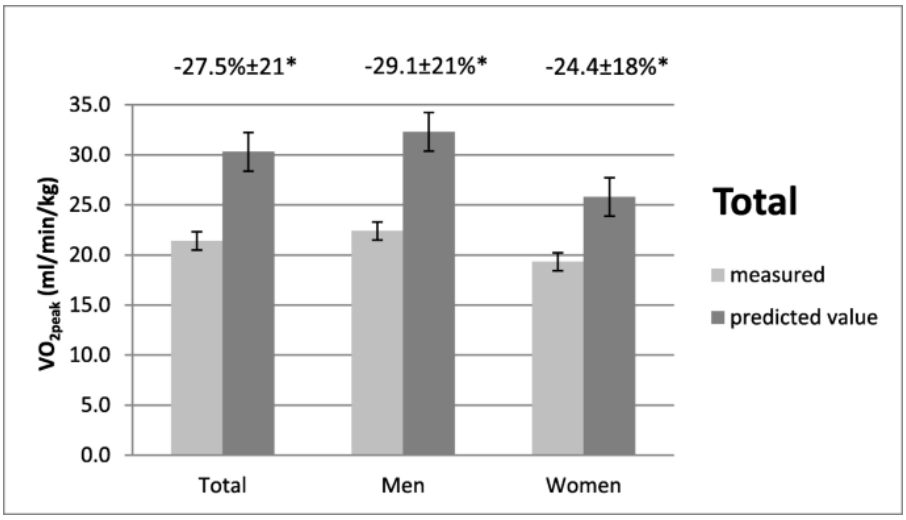

Fig. 2 Comparison of measured VO_{2peak} values with gender- and age-matched healthy reference VO_{2peak} values in total, men and women. * = significant difference to measured VO_{2peak} and reference values $p < 0.005$

For the overall sample, VO2peak was on average 21.4 ml/min/kg, with a value of 22.4 ± 5.9 ml/min/kg for men and 19.3 ± 4.7 ml/min/kg for women. Figure 2 presents the comparison with age- and gender-matched reference values [14]. For the total sample, it was apparent that the VO2peak values were significantly reduced (− 27.5 ± 20.8%, p < 0.001). The deviation of VO2peak from gender- and age-

matched healthy reference values was slightly larger in men (− 29.1 ± 21.6%, p < 0.001) than in women (− 24.4 ± 18.1%, p < 0.001), with no significant difference between the two groups (− 4.7%, p = 0.146).

Hemoglobin at the day of CPET was higher in men (11.9 ± 1.8 g/dl) than in women (11.3 ± 1.5 g/dl), however there was no statistically difference between men and women (men vs woman 4.7%, p = 0.766). Hemoglobin values were below the normal range.

Table 2 shows the deviation of VO2peak from healthy reference values, the measured VO2peak values, the amount of cardio toxic agents, and the activity level per week (MET) in the year before diagnosis depending on different age groups. The age group between 46 and 55 years demonstrated the largest deviation from healthy reference values (− 36.6% ± 16.7), whereas the eldest (60–75 years) illustrated the smallest deviation (− 11.8% ± 15.9). The amount of cardio toxic agents was highest in the youngest age group (1.9 ± 1.3) with small differences to the other age groups, whereas the oldest participants notably received the least amount (0.9 ± 1.9).

Table 2 Comparison of measured VO_{2peak} (ml/kg/min) values and the healthy gender-age-matched reference VO_{2peak} values in total, n_Cardiotox, METh/week

Age group (years)	n	Deviation VO_{2peak} from healthy reference (%) mean ± SD	VO_{2peak} (ml/kg/min) mean ± SD	n_Cardiotox mean ± SD	METh/week mean ± SD
18-35	18	-25.1 ± 15.7	24.7 ± 6.3	1.9 ± 1.3	3.3 ± 5.4 (n = 6)
36-45	13	-31.7 ± 18.7	23.9 ± 7.4	1.5 ± 1.4	8.1 ± 13.9 (n = 4)
46-55	59	-36.6 ± 16.7	20.2 ± 5.6	1.7 ± 1.4	6.1 ± 13.1(n = 14)
56-65	80	-25.4 ± 22.9	21.7 ± 5.5	1.4 ± 1.2	9.2 ± 17.5 (n = 27)
66-75	24	-11.8 ± 15.9	19.1 ± 4.1	0.9 ± 1.9	9.2 ± 14.8 (n = 9)

N, number of patients; *MET*, metabolic equivalent of task; *HCT-CI*, comorbidity index by Sorror

Factors explaining CRF

A total of 183 patients could be included in the multiple regression analysis. The analysis reveals age, female gender, BMI, n_Cardiotox, Hemoglobin_auc, and physical activity prior to diagnosis as predictors with a significant influence on VO_{2peak}, whereas the HCT-CI, the amount of transplantations (n_Transplantations), and t_Therapies had no significant impact. The R^2 was 40% (Table 3).

Table 3 Multiple regression of determinants VO_{2peak} (ml/min/kg) $R^2 = 40\%$, n = 183

	β	*p*	95% CI
Gender	-3.01	.000	-4.44;-1.58
Age	-.11	.003	-.17;.05
BMI	-.44	.000	-.58;-0.31
t_Therapies	.11	.146	-.04;.27
n_Cardiotox	-.73	.015	-1.33; -.11
HCT-CI	-.34	.138	-.79;.11
Hemoglobin_auc	.56	.004	.18;.93
n_Transplantations	.45	.658	-.89;1.78
Physical activity	.10	.000	.05;-.14

BMI, body mass index; *HCT-CI*, comorbidity index by Sorror; *CI*, confidence interval

Factors explaining deviation of CRF from normative values

Regression analysis for the deviation of VO_{2peak} from healthy reference values shows that age, gender, BMI, Hemoglobin_auc, and physical activity prior to diagnosis are significant determinants. The explaining variance is 26% (Table 4).

Table 4 Multiple regression of determinants deviation VO_{2peak} (ml/min/kg) from healthy reference (%)
$R^2 = 26\%$, n = 183

	β	*p*	95% CI
Gender	7.58	.001	1.72;13.43
Age	.043	.000	.19;.67
BMI	-1.12	.000	-1.68; - .57
t_Therapies	.13	.673	-.48;.75
n_Cardiotox	-2.46	.047	-4.89;-.36
HCT-CI	-.30	.750	-2.15;1.55
Hemoglobin_auc	1.99	.001	.46;3.52
n_Transplantations	1.56	.575	-3.91; 7.02
Physical activity	0.41	.000	.22;.60

BMI, body mass index; *HCT-CI*, comorbidity index by Sorror; *CI*, confidence interval

Discussion

Our study demonstrates decreased CRF in allo-HSCT candidates prior to transplantation. Results indicate that patients at higher age, of female gender, with low hemoglobin values, who received cardio toxic treatment prior to allo-HSCT, and have a low physical activity are of risk for lower CRF. Considering gender- and age-matched healthy VO_{2peak} reference values, men as well as patients with a younger age have a higher risk for lower CRF. A higher BMI and lower physical activity was a significant predictor for low CRF in both regression models.

Reduced physical performance levels prior to HSCT has been found in various studies [7, 8, 16, 17]. However, comprehensive data and analyses procedures are missing to identify patients at risk and to assess the clinical significance of reduced CRF. In comparison with reference values of healthy adults, the VO_{2peak} of our sample was significantly reduced by −27.5% which was quite similar to other studies in the field [7, 8]. This is further in accordance with findings of impaired respiratory and skeletal muscle strength as well as reduced submaximal exercise capacity in patients prior to allo-HSCT [16,17,18]. In comparison with other severely impacted and treated patient groups like pancreatic cancer patients, the deviation from the healthy reference group was higher [19], whereas breast cancer patients at the same age interestingly showed lower VO_{2peak} values [20].

Since reduced CRF level is associated with poor prognosis after HSCT [8], but on the other hand can be positively modified by exercise therapy [21, 22], it is of clinical relevance to detect patient-related predictors in order to identify low CRF patients and to treat them as early as possible in accordance with the prehabilitation approach [23]. Regarding patient-related predictors, we were able to show that the amount of chemotherapies with cardio toxic ingredients received prior to allo-HSCT is a predictor of low CRF. In light of the fact that 24.2% of our population received one or more transplantation prior to allo-HSCT, which frequently include cardio toxic agents and affect cardiac function [24, 25] such an observation seems to be plausible [26]. Interestingly, although the number of received cardio toxic treatments could explain variation in CRF, the majority of our population (90%) showed good LVEF values indicating no major structural impact on the heart muscle. The detection of heart damage after exposure to potentially cardio toxic chemotherapeutic agents is complex and requires various assessment procedures [27] and was not performed within this study. Nevertheless, an explanation for this finding could be that assessments without exercise-induced cardiovascular stress, like a resting echocardiography, are not sensitive enough to detect preliminary heart damage [7]. In addition, it is conceivable that the toxic components of chemotherapies change intramuscular capillary density and mitochondrial content, and therefore reduce the oxygen extraction from the blood to the muscles, leading to reduced VO_{2peak} values [28]. Causes of muscle dysfunction in cancer patients are complex and very little is known about adaptions at the muscle structural level [29]. However, improved muscle strength seems to have an impact on peak work rate in a CPET, but not on VO_{2peak} in pancreatic cancer patients. This could also be explained by peripheral intramuscular changes and increase in cross-sectional areas of muscle fibers [30]. Further interpretations are difficult, because measures of muscle strength were not part of our present analysis. However, our

data show that it may be worthwhile to carry out further investigations including measures of muscle strength.

Not unexpected, we showed that low levels of hemoglobin for at least 3 months prior to allo-HSCT were another predictive factor for low CRF. Reduced hemoglobin levels as a result of reduced bone marrow capacity due to the disease itself or chemotherapy treatment could limit oxygen delivery to exercising muscles and could affect CRF [31]. Low hemoglobin is associated with a lower quality of life and functional capacity [32] and is a prognostic factor for overall survival and disease-free survival in several hematological malignancies [33].

Further, gender had a significant impact on CRF. Women had lower VO_{2peak} values than men, which is a well-known gender-related finding [34]. However, men showed slightly greater, but non-significant deviations, from heathy reference values than women (−29.1% vs −24.4%). This is not in line with findings of other comparable studies [8], but was similarly reported in solid cancer patients [19].

Regarding age, we found that patients between 46 and 55 years revealed reduced CRF, whereas the oldest age group (66–75 years) had the lowest deviation from healthy norm values. An explanation for this finding could be related to the fact that older patient groups mostly receive dose-reduced therapies [35] compared with younger patients and therefore experience lower grades of myelosuppression and hematotoxicity. Otherwise, older cancer patients might be at increased risk of chemotherapy-related cardiotoxicity due to physiologic changes of several organ systems [36] or reduced tolerance of drug toxicity due to lower lean mass [37]. However, age- and treatment-associated variables are independently explaining variation in CRF and therefore seem to be both important for identifying patients with low CRF.

As expected, our data in both regression models show that physical inactivity prior to allo-HCT affects CRF negatively. In observational studies, it could be shown that a higher level of physical activity has a positive influence on the treatment process [38], which may additionally promote CRF even before allo-HSCT. Additionally, our models show that patients with higher BMI had a significantly lower CRF. This finding could be partially explained due to the fact that body weight is part of both formulas (BMI and VO_{2peak}/ml/min/kg, respectively). Furthermore, the increased body mass also requires more oxygen during exercise, leading to reduced values. In allo-HSCT patients, both under- and overweight were associated with increased risk for complications and lower overall survival [39]. However, drawing conclusions from BMI regarding the association to CRF is difficult because the BMI gives no detailed information on the distribution of fat mass and muscle mass. In the field of allo-HSCT, for example, pre-transplant weight loss has been shown to be a prognostic variable [40].

Based on our analyses, we were able to identify and characterize patients with low CRF prior to allo-HSCT. Past studies have shown that reduced CRF predicts symptom severity and mortality in patients undergoing allo-HSCT [8, 18]. Consequently, we recommend based on our data a targeted

exercise program to create the best possible condition for allo-HSCT. This would lead to a prehabilitation approach and is in line with current recommendations from the literature, "getting fit for allogeneic hematopoietic cell transplantation" [41]. Beneficial examples for prehabilitation in cancer patients exist [42, 43], but are totally understudied in hematological patients prior to allo-HSCT. Nevertheless, exercises have the potential to improve CRF in patients preparing to undergo HCT [23], which is potentially crucial for survival and for reducing treatment-related side effects [44, 45]. Our data reinforce timely supportive care with exercise and identify needy subgroups in allo-HSCT candidates. For a better planning of exercise therapies, patients with low physical activity level, who are middle-aged, who have a high BMI, who had received cardio toxic agents, and who have chronic low hemoglobin levels should be the targeted population.

Our investigation has several limitations. The retrospective analysis was based on data of a randomized exercise intervention trial and therefore was not stratified and designed to evaluate baseline characteristics concerning potentially influencing factors with regard to CRF in patients prior to allo-HSCT. This might have also led to a preselection of a population with a potential affinity to exercise. Further, clinical data prior to allo-HSCT was extracted from the medical records which led to incomplete information.

This investigation also has several strengths. To our knowledge, the study sample of PETRA participant is currently the largest providing comprehensive cardiorespiratory fitness data applying gold standard assessment. Due to the large sample size, it was possible to identify influencing factors, which allow a more profound understanding of patients' performance status and its influencing parameters prior to allo-HSCT.

In conclusion, our findings demonstrated considerable reduction of CRF in patients immediately prior to allo-HSCT. We found that high BMI, low physical activity, amount of cardio toxic agents, and low hemoglobin level negatively impact CRF prior to allo-HSCT. Since CRF is proposed to be an independent risk factor for transplant outcome, strategies to modify CRF prior to allo-HSCT might be worthwhile to follow. Therefore, structured individualized aerobic exercise intervention programs should be recommended for increasing CRF prior to allo-HSCT. Based on our findings, describing risk factors for low CRF prior to allo-HSCT could lead to a targeted prehabilitative exercise intervention approach identifying those patients with highest needs.

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Conflict of interests
The authors declare that they have no conflict of interest.

Ethical approval

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

Consent to participate

All patients provide written informed consent.

Consent for publication

All patients provide written informed consent.

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4 MANUSCRIPT II

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Author Contributions

M.L.: collection and assembly of data, statistical analysis and interpretation of the data, wrote the main manuscript
R.K.: collection and assembly of data, critical review of the manuscript
M.K.: critical review of the manuscript, statistical analysis and interpretation of the data
P.D.: provision of study materials or patients, critical review of the manuscript
T.L.: provision of study materials or patients, critical review of the manuscript
M.B. conception and design of the study, critical review of the manuscript
J.W.: conception and design of the study, provision of study materials or patients, statistical analysis and interpretation of the data, critical review of the manuscript
All authors reviewed the manuscript and approved the submitted version.

Factors affecting pretransplant muscle strength in allogeneic stem cell transplant candidates prior transplantation

Running Title:

Factors of muscle strength prior allo-HCT

(M.A.) Limbach, Matthias[1,2]; (Dr.) Kuehl, Rea[1]; (M.A.) Koeppel, Maximilian[1,2]; (Prof.) Dreger, Peter[3]; (Prof.) Luft, Thomas[3]; (Prof.) Bohus, Martin[4]; (Prof.) Wiskemann, Joachim[1,2]

[1] Department of Medical Oncology, National Center for Tumor Diseases (NCT), Heidelberg University Hospital, Germany
[2]Institute of Sports and Sport Science, Heidelberg University, Im Neuenheimer Feld 700, Heidelberg, Germany
[3]Department of Medicine V, Heidelberg University Hospital, Germany
[4]Central Institute of Mental Health, Mannheim, Germany

Abstract

Purpose Physical performance is crucial for prognosis after allogeneic hematopoietic stem cell transplantation (allo-HCT). Cardiorespiratory fitness has already been shown to have prognostic value and there is increasing evidence that muscle strength and associated parameters (e.g. sarcopenia) are also of clinical relevance. Therefore, there is a need for the quantification of muscle strength and defining risk factors for reduced performance values.

Methods Maximal voluntary isokinetic (MVIC) and isometric (MIPT) muscle strength was assessed 2.4 ± 7.1 days prior admission for allo-HCT with a stationary isokinetic testing machine (IsoMed2000). We calculated percentiles for knee extension and hip flexion using healthy reference values. Regression models were used to identify predictors for reduced muscle strength including gender, age, body mass index (BMI), number of previous cardiotoxic therapies, number of previous transplantations, Comorbidity Index (HCT-CI), hemoglobin level and physical activity.

Results Data of 212 patients revealed considerably deviations from healthy reference values. Patients were located in the following percentiles: MVICKnee 37.5 ± 30.3, MVICHip 39.5 ± 31.3 and MIPTKnee 22.9 ± 26.5; MIPTHip 22.6 ± 27.4. Sub-group analyses showed that patients with younger age and male gender possess the highest deviations. Muscle strength values were significantly ($p < 0.05$) influenced by age, female gender, lower BMI and higher HCT-CI.

Conclusion Muscle strength is considerably reduced immediately prior to allo-HCT. Identified patient characteristics for reduced muscle strength point to the population that should be primarily targeted with exercise respectively resistance training interventions prior to allo-HCT to contribute to a well prepared transplant candidate.

Keywords Exercise; Allogeneic Stem Cell Transplantation; Oncology; Muscle Strength; Pretransplantation.

Introduction

Allogeneic stem cell transplantation (allo-HCT) is a curative therapy for a variety of malign hematopoietic disorders. Although remarkable therapeutic successes due to enhanced treatment techniques and supportive care lead to an improved outcome and even older or comorbid patients can be treated, there is a substantial risk of therapy-related morbidity and mortality[1, 2]. Because of the intensive and demanding treatment, the determination of appropriate candidates for allo-HCT is crucial, as is the identification of risk factors that potentially influence the outcome[3]. It is assumed, that physical performance in general[3], but also specifically cardiorespiratory fitness (CRF), is an important and potentially predictive indicator for symptom burden and mortality in alloHCT-candidates[4]. Besides CRF, various limitations related to the strength performance of the skeletal muscle also appear to be crucial for cancer patients[5, 6]. In allo-HCT candidates it has been revealed that significant muscle weakness and limitations in muscle strength exist after allo-HCT[7] as well as prior allo-HCT[8]. Furthermore, sarcopenia, defined as a loss of muscle mass and muscle strength, has become apparent to be associated with a significantly increased risk of poor outcome even in allo-HCT candidates[9, 10]. Thus, it is reasonable to assume that muscle strength could be a crucial influencing factor that needs to be described and comprehensively evaluated in the light of allo-HCT. Therefore, we aimed to determine muscle strength of various muscle groups in allo-HCT candidates by using the gold-standard approach of stationary isokinetic dynamometry and aimed to identify influencing factors for reduced muscle strength performance.

Patients and Methods

Setting and Patients

We analyzed baseline data from 212 allo-HCT patients from the study *Physical Exercise Training versus Relaxation in Allogeneic stem cell transplantation* (PETRA)[11], a large two-arm randomized controlled trial (RCT). All patients, scheduled for an allo-HCT at the Heidelberg University Clinic, of age ≥18 years and able to understand and follow the study protocol, were eligible for enrollment in the PETRA trial. Exclusion criteria were inability to walk or stand, instable bone lesions, severe neurological deficiencies, severe cardiac or cardiovascular diseases, and severe overall pulmonary insufficiency. Baseline data were obtained prior to admission for allo-HCT. After baseline assessments the participants were randomized either to a supervised exercise group or a supervised progressive muscle relaxation group. Both interventions were scheduled for one year, with a follow-up measurement 2 years after allo-HCT. Primary endpoint is 2-year overall survival. The study has been approved by the ethic committees of the Ethic Committee II of the University of Mannheim (number 2009–349 N-MA) and the Ethic Committee of the University of Heidelberg (number S-021/2011) and is registered at ClinicalTrials.gov (NCT01374399). All patients provide written informed consent.

Determination of the muscle strength

Isokinetic and isometric muscle strength was measured by using the IsoMed 2000-system B-series version (D&R Ferstl GmbH, Hemau, Germany). The reliability and validity of this measurement has been reported in serval studies[12-14] and isometric and isokinetic assessments are considered as gold standard method to measure muscle strength[5]. Furthermore, it was successfully applied in various cancer populations[15-18]. Our test protocol includes the assessment of the maximal voluntary isometric contraction (MVIC) and the maximal isokinetic peak torque (MIPT) of knee extensors and hip flexors. The measured torques are reported as Newton meter (Nm).

During test protocols, both the subject and the instructor were able to see the strength curve on the monitor. Subjects were given verbal encouragement to generate the highest possible strength. To minimize extraneous body movements, subjects were fixed by straps (thigh, pelvic, torso) and used handlebars during assessment of extensors and flexors of the knee. Each torque artefact resulting from deceleration, which often exceeds the true peak torque, was removed by using a filter; only gravity-corrected data were used for analysis.

Assessment of MVIC

Maximal voluntary isometric contraction (MVIC) was tested bilaterally for knee extensor (angle position 36°) and hip flexor (angle position 33°), which consistently were the strongest angle positions each. Patients were requested to exert maximum force against an insurmountable resistance and to hold it for 6 seconds.

Assessment of MIPT

Maximal isokinetic peak torque (MIPT) was assessed bilaterally for extensors and flexors of the knee and hip. Range of motion for isokinetic measurements varied from 10° to 90° flexion in the knee (straight leg is 0°) and from 10° to 100° in the hip (straight leg in dorsal position is 0°). Patients were instructed to move the machine arm for 10 repetitions as firmly and as fast as possible in the alternating direction between extension and flexion with constant angular velocity (60°/s). The highest torque value of all cycles at considered joint side was analyzed.

Descriptive and influencing variables for muscle strength

We investigated potentially influencing factors for MVIC and MIPT. Congruent with our previous analysis on cardiorespiratory fitness[19] these were: age, gender, body mass index (BMI), total number of transplantations (allogeneic and autologous, n_Transplantations), number of previous cardiotoxic therapies (n_cardiotox), months between last treatment to allo-HCT (T_Therapies), the Hematopoietic Cell Transplantation-specific Comorbidity Index (HCT-CI), physical activity and hemoglobin levels. Further, we gathered information on primary hematological malignancies and the proportion of myeloid and lymphatic malignancies, Karnofsky Performance Status (KPS), and months between primary diagnoses to allo-HCT (T_Diagnosis).

Potentially influencing variables and clinical data were extracted from patient's medical records. BMI was calculated as body weight divided by square of height in meters. HCT-CI was determined according to guidelines and separated into low to intermediate risk group (<3) and high risk group (≥3)[20]. The degree of physical activity was operationalized with metabolic equivalent of task (MET). MET hours per week (MET × h/week) were calculated by summing the average of self-reported hours per week spent in walking, cycling, or other physical activities. Hemoglobin (g/dl) level was measured on the day of muscle strength assessment. Lastly, we calculated the area under the curve values for hemoglobin levels over the last 3 months prior allo-HCT (Hemoglobin_auc).

Statistical analyses

Clinical and demographic data were reported by descriptive analysis and are reported as mean ± SD and range. Expected muscle strength values were calculated by the formula of Danneskiold-Sam (2009)[21] for healthy individuals considering age and gender distribution. Muscle strength values were presented as percentiles to illustrate the deviation to the healthy reference collective, whereas the 50th percentile represents the median of the reference sample.

Hemoglobin-level over the last three month was calculated as area under the curve (AUC) score using the trapezoidal rule[22]. To identify determinants of muscle strength prior allo-HCT, a multivariate regression analysis was conducted. In consideration of multicollinearity, we aimed to identify the most relevant determinants. The following independent variables were entered into the logistic regression model simultaneously: age, gender, BMI, n_Transplantations, n_Cardiotox, t_Therapies, HCT-CI, Physical activity and Hemoglobin_auc. We chose the muscle strength of the quadriceps muscle as a representative value for loads of activities of daily living. The values of MVIC and MIPT were defined as dependent variable: $MVIC_{Knee}$ and $MIPT_{Knee}$. Significant level was set at $p<0.05$. Data were analyzed using IBM SPSS v. 26 and R version 4.0.

Results

Five hundred forty-four patients were screened and n = 99 were ineligible for the study due to exclusion criteria (18.2%). From n = 445 (81.8%) eligible patients n = 178 (40%) did not participate due to no interest (n = 94, 52.8%), organizational problems (postponement, no exercise testing capacity available due to short notice admission to allo-HCT; n = 39, 21.9%) and n = 45 (25.3%) because of other reasons. Two hundred sixty-seven patients were included in the study of whom n = 212 participated in the assessments of MVIC and MIPT. Major reasons for not being able to perform this strength testing can be seen in Figure 1. No (serious) adverse events occurred.

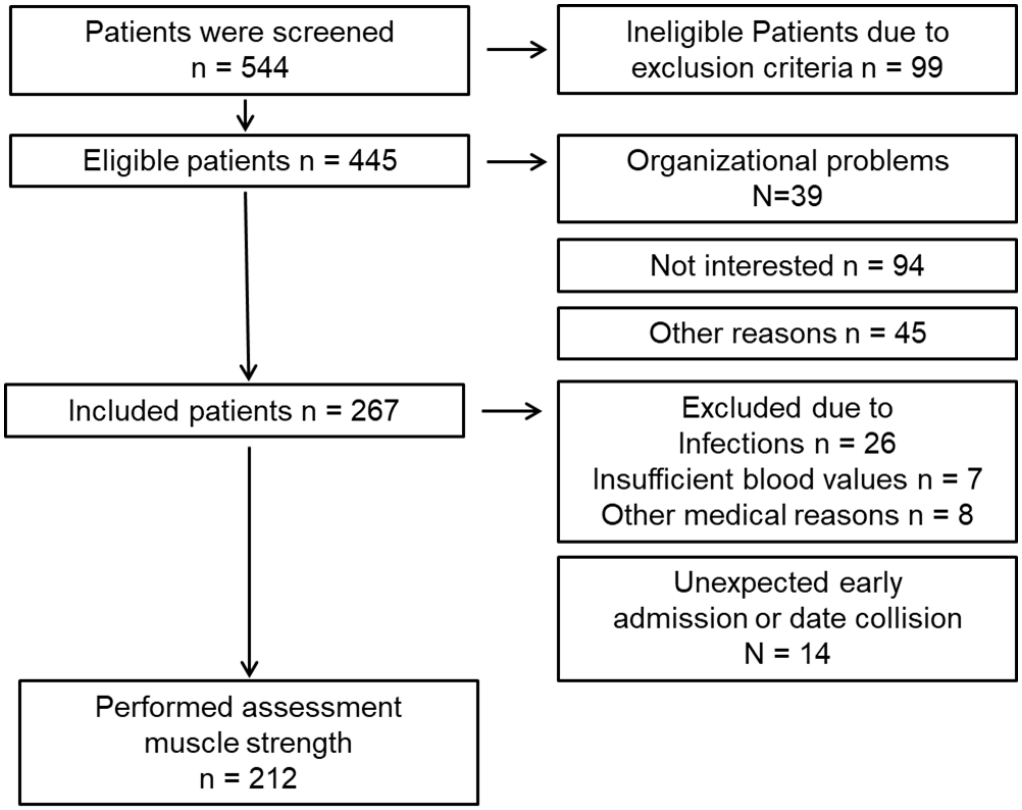

Fig.1 Patient flow chart showing the number of patients who were available for muscle strength assessment

Clinical data and demographics of study participants who performed MVIC and MIPT are described in Table 1. Patients had a mean age of 54.49 ± 11.4 years and main diagnosis was acute leukemia (AML, 29.1%). Participants were on average 36.2 ± 48 months after main diagnosis and 54 patients (25.6%) received one or more previous transplantations. Mean hemoglobin at the day of physical assessment was 11.6 ± 1.9 (g/dl) and hemoglobin level during the last three months (Hemoglobin_auc) was 11.3 ± 1.9 (g/dl) and therefore below the normal range. On average, the patients performed the measurements 2.4 ± 7.1 days prior admission to allo-HCT.

Table 1 Baseline descriptive data

	n	Mean	SD	Range
Age (yr) at diagnosis	212	54.49	11.4	18-75
Gender, n (%)	212 (100)	-	-	-
Males	143 (67.5)			
Females	69 (32.5)			
BMI (kg/m^2)	212	26.41	4.5	17-45
Diagnosis, n (%)	210 (100)	-	-	-
AML	61 (29.1)			
ALL	12 (5.7)			
CLL	39 (18.6)			
MM	24 (11.4)			
CML/MPS	18 (8.6)			
MDS	19 (9.1)			
other Lymphoma	34 (16.2)			
other	3 (1.4)			
Missing	2 (0.9)			

Time from diagnosis to alloHSCT (month) Missing	210 2	36.2	48.0	0-328
Time between exercise test to admission alloHSCT (days)	212	2.4	7.1	0-47
HCT-CI (n) <3 ≥3 Missing	200 173 27 12	0.91	1.4	0-7
KPS (n) <90 ≥90 Missing	207 23 184 5	91.48		100-70
Hemoglobin value day of testing (g/dl)	212	11.6	1.9	6.8-17.0
Remission status prior alloHSCT (%) CR PR No CR Unknown Missing	211 (100) 75 (35.5) 77 (36.5) 55 (26.1) 4 (1.9) 1 (0.5)	-	-	-
Smokers (%) Current Ever Year before diagnosis Never Missing	196 (100) 9 (4.2) 68 (32.1) 29 (13.7) 98 (46.2) 8 (3.8)			
Time since last therapy (month)	212	2.9	7.5	0-88
Physical activity Missing	208 4	7.9	15.5	0-99.5
Hemoglobin last 3 month (g/dl) Missing	209 3	11.3	1.9	6.5-15.7
Amount of cardio toxic agents	210	1.5	1.4	0-9
Number of previous transplantations Received one or more transplantation Missing	211 54 1	0.32	0.6	0-3

Abbreviations: N=Newton; n = Number of Patients; BMI = body mass index; HCT-CI = Comorbidity Index by Sorror; KPS = Karnofsky Performance Status; allo-HCT = allogeneic stem cell transplantation; CR = Complete remission; PR = Partial remission; AML = acute myeloic leukemia; ALL = acute lymphocytic leukemia; MM = multiple myeloma; CML = chronic myeloid leukemia; MPS = myeloproliferative syndrome; MDS = myelodysplastic syndrome.

Description of muscle strength values for MVIC

Muscle strength assessments demonstrated mean values for $MVIC_{Knee}$ (n=212) of 159.7 ± 48.3 Nm. Men (n = 143) reached 178.4 ± 45.6 Nm whereas 120.9 ± 25.6 Nm were measured for the women (n = 69). Mean values for $MVIC_{Hip}$ (n = 203) were 129.72 ± 44.48 Nm. Men (n = 140) had values of 143.82 ± 43.2 Nm and women (n = 63) achieved values of 92.36 ± 28.56 Nm.

Description of muscle strength values for MIPT

For $MIPT_{Knee}$ we obtained mean values of (n = 211) 118.6 ± 40.3 Nm, with males (n = 143) reaching 134.0 ± 40.3 Nm and females (n = 68) achieving 86.7 ± 20.7 Nm. $MIPT_{Hip}$ (n = 201) measured 100.1 ± 38.81 Nm. Men (n = 139) obtained values of 110.54 ± 37.1 Nm and women (n = 62) of 76.41 ± 22.7 Nm.

Muscle strength (MVIC and MIPT) in relation to healthy reference values

On average, assessed patients were located between the 37th and 40th reference percentile ($MVIC_{Knee}$ 37.5 ± 30.3, $MVIC_{Hip}$ 39.5 ± 31.3). The proportion of patients below the median (50th percentile) of the reference group is for both $MVIC_{Knee}$ and $MVIC_{Hip}$ at 66%. On average, the reference percentiles results for $MIPT_{Knee}$ were 22.9 ± 26.5 respectively 22.6 ± 27.4 for $MIPT_{Hip}$, resulting in a proportion of 84% ($MIPT_{Knee}$) and 83% ($MIPT_{Hip}$) under the 50th reference percentile.

Figure 2 demonstrates the deviation of the measured MVIC values as percentiles from the calculated healthy reference values depending on a) male and female gender and for the different b) age groups. In general, men showed a higher deviation than women in all investigated aspects. Concerning age, the younger patients, in particular <20 years and 20-29 reveal the higher deviations and seem to be most affected in their physical strength performance.

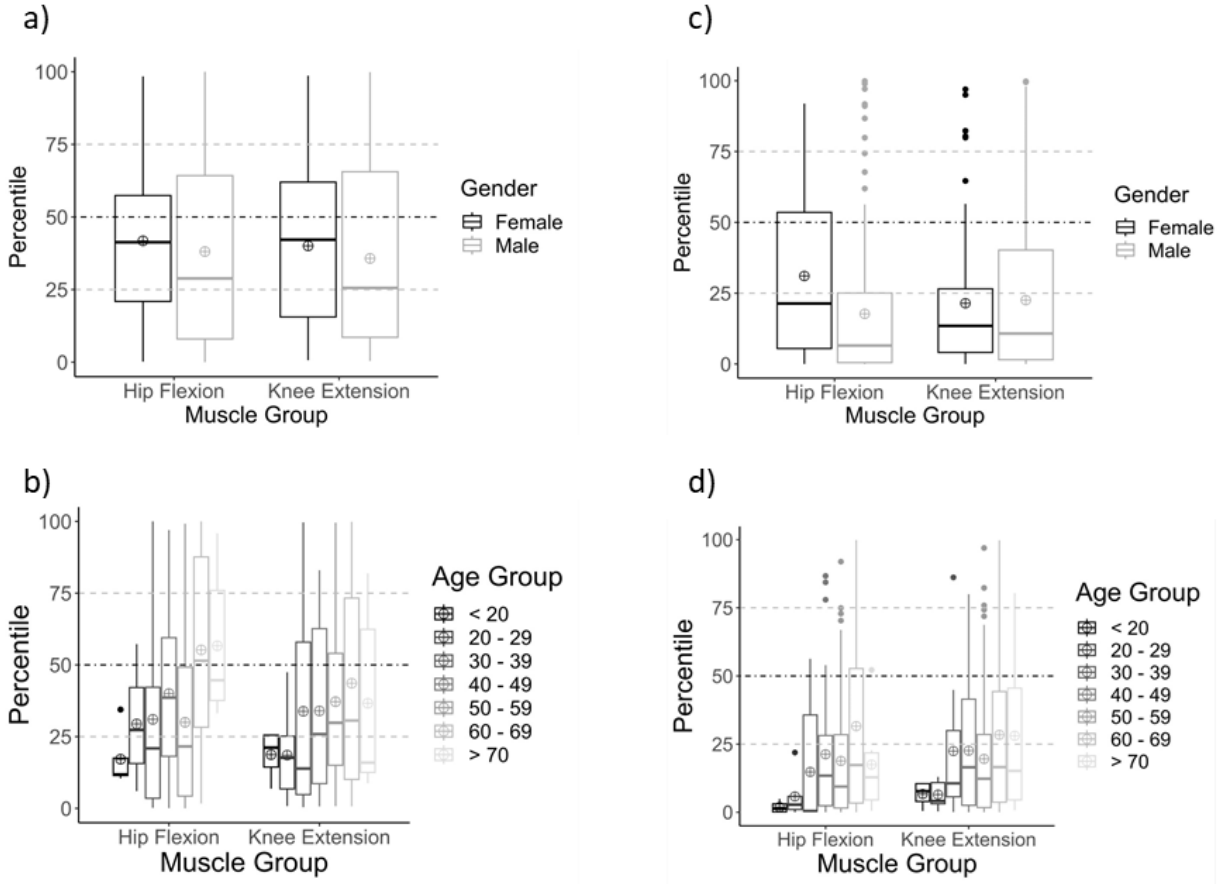

Fig. 2 Reference percentiles of MVIC values for gender (a) and age group (b) and reference percentiles of MIPT 60°/s values for gender (c) and age group (d). – = median line, ⊕ = mean

Parts c) and d) of figure 2 show the deviation of the measured MIPT values from the calculated healthy reference values according to the c) female and male gender and to the different d) age groups. With regard to the muscle groups, the values of "hip" and "knee" demonstrate higher muscle performance of women. Men demonstrate a higher deviation from healthy reference values than women in the hip flexion, whereas the mean values in the knee extension are nearly congruent for both genders. Taking patients´ age into account, all age groups show a strong limitation of performance. Patients with ages <20 reveal the highest deviation in hip values, but also the ages of 20 and 39 show substantial deviations. Focusing on the knee values, the younger patients between <20 and the ages of 20 and 29 display the greatest difference compared to their healthy peers.

Factors affecting muscle strength ($MVIC_{Knee}$ and $MIPT_{Knee}$)

Regression analysis for $MVIC_{Knee}$ shows that higher age, female gender and lower BMI are significant determinants for low MVIC. The explaining variance is 42.3%. The analysis for $MIPT_{Knee}$ reveals that higher age, female gender, lower BMI and higher HCT-CI are significant factors with an explaining variance of 46.7% (Table 2).

Table 2 Multiple regression of the determinants of muscle strength: $MVIC_{Knee}$ and $MIPT_{Knee}$ for 60°/s.

$MVIC_{Knee}$ (Nm) R^2 = 42.3% , n = 192, p = .000			
	β	*p*	95% CI
Gender	-.570	.000	-71.220; -47.308
Age	-.249	.000	-1.564; -.562
BMI	.173	.004	.605; 3.137
T_Therapies	.111	.072	-.104; 2.382
n_cardiotox	-.109	.115	-8.709; .954
HCT-CI	-.091	.118	-7.163; .814
Physical activity	.039	.528	-.255; -.495
n_Transplantations	.032	.638	-8.222;13.389
Hemoglobin_auc	.036	.546	-2.152; 4.058
$MIPT_{Knee}$ (Nm) R^2 = 46.7% , n = 191, p = .000			
	β	*p*	95% CI
Gender	-.570	.000	-59.023; -39.810
Age	-.278	.000	-1.388; -.0583
BMI	.174	.003	-.550; 2.574

T_Therapies	.080	.177	-.311; -1.677
n_cardiotox	-.093	.163	-6.615; 1.121
HCT-CI	-.114	.043	-6.496; -.111
Physical activity	.070	.232	-118; 482
n_Transplantations	.032	.625	-6.493; 10.784
Hemoglobin_auc	.113	.052	-.018; 4.961

MVIC = maximal voluntary isometric contraction;MIPT = maximal isokinetic peak torque; BMI = bodymass index (kg/m²); T_Therapie = months between last treatment to allo-HCT; n_cardiotox = number of previous cardiotoxic therapies; HCT-CI = comorbidity index by Sorror; n_Transplantations = total number of transplantations; CI = confidence Interval; Physical activity (MET); Hemoglobin_auc = hemoglobin levels over the last 3 months (g/dl) prior allo-HCT; Nm= Newton metre.

Factors affecting muscle strength deviation in comparison to reference values ($MVIC_{Knee}$ and $MIPT_{Knee}$)

Regression analysis for $MVIC_{Knee}$ shows that lower BMI and the HCT-CI were significant determinants for low MVIC. The explained variance (R^2) was 13.1%. Analysis for $MIPT_{Knee}$ reveals also that lower BMI values und and higher HCT-CI values were significantly explaining factors with an overall R^2 19.3% (Table 3).

Table 3 Multiple regression of the determinants of muscle strength deviation from reference values: $MVIC_{Knee}$ and $MIPT_{Knee}$ for 60°/s.

$MVIC_{Knee}$ (Nm) R^2 = 13.1% , n = 177, p = .005			
	β	*p*	95% CI
Gender	-.043	.583	-71.220; -47.308
Age	.129	.096	-1.564; -.562
BMI	.165	.033	.605; 3.137
T_Therapies	.151	.071	-.104; 2.382
n_cardiotox	-.117	.204	-8.709; .954
HCT-CI	-.160	.033	-7.163; .814
Physical activity	-.034	.675	-.255; -.495
n_Transplantations	.129	.155	-8.222;13.389
Hemoglobin_auc	.056	.477	-2.152; 4.058
$MIPT_{Knee}$ (Nm) R^2 = 19,3% , n = 184, p = .000			
	β	*p*	95% CI
Gender	.134	.059	-59.023; -39.810
Age	.124	.053	-1.388; -.0583

BMI	.224	.002	.550; 2.574
T_Therapies	.076	.305	-.311; -1.677
n_cardiotox	-.128	.136	-6.615; 1.121
HCT-CI	-.167	.019	-6.496; -.111
Physical activity	.107	.151	-118; 482
n_Transplantations	.003	.937	-6.493; 10.784
Hemoglobin_auc	.135	.066	-.018; 4.961

MVIC = maximal voluntary isometric contraction;MIPT = maximal isokinetic peak torque; BMI = bodymass index (kg/m²); T_Therapie = months between last treatment to allo-HCT; n_cardiotox = number of previous cardiotoxic therapies; HCT-CI = comorbidity index by Sorror; n_Transplantations = total number of transplantations; CI = confidence Interval; Physical activity (MET); Hemoglobin_auc = hemoglobin levels over the last 3 months (g/dl) prior allo-HCT; Nm= Newton metre.

Muscle strength in various subgroups

Table 4 shows descriptive muscle strength values for $MVIC_{Knee/kg}$ and $MIPT_{Knee/kg}$ $MVIC_{Knee}$ and $MIPT_{Knee}$ for 60°/s. for various clinical parameters. Overall, no distinctive subgroups could be identified, but slight tendencies can be depicted.

Table 4 Muscle strength performance values for clinical subgroups

Variable (n MVIC, n MIPT)	$MVIC_{Knee/kg}$ (Nm) Mean ± SD	$MIPT_{Knee/kg}$ (Nm) Mean ± SD	$MVIC_{Knee}$ (Nm) Mean ± SD	$MIPT_{Knee}$ (Nm) Mean ± SD
Diagnosis				
AML (n=61)	1.99 ± 0.49	1.49 ± 0.41	156.9 ± 47.2	118.1 ± 40.2
ALL (n=12)	1.91 ± 0.54	1.28 ± 0.28	136.5 ± 45.2	95.6 ± 28.4
CLL (n=39)	2.01 ± 0.45	1.52 ± 0.41	161.9 ± 42.1	123.4 ± 39.2
MM (n=24)	1.84 ± 0.64	1.35 ± 0.45	159.4 ± 60.8	117.3 ± 42.4
CML/MPS (n=18, n=17)	2.22 ± 0.39	1.58 ± 0.27	172.7 ± 37.5	126.3 ± 32.5
MDS (n=19)	1.88 ± 0.53	1.31 ± 0.38	156.8 ± 52.8	108.4 ± 36.3
Other Lymphoma (n=34)	2.08 ± 0.51	1.57 ± 0.57	164.2 ± 52.5	124.9 ± 47.3
Other (n=3)	1.66 ± 0.25	1.07 ± 0.29	137.5 ± 30.1	87.5 ± 21.1
Malignancy				
Myeloid (n=101)	2.01 ± 0.49	1.47 ± 0.38	158.8 ± 46.8	116.7 ± 38.0
Lymphatic (n=109)	1.98 ± 0.52	1.48 ± 0.44	160.5 ± 49.9	120.5 ± 42.2
Missing (n=2)				
Received no prior transplantation (n=157, n=156)	1.98 ± 0.48	1.46 ± 0.41	158.7 ± 45.4	117.6 ± 38.6
Received one or more prior transplantations (n=54)	2.02 ± 0.58	1.51 ± 0.44	161.3 ± 56.3	120.7 ± 44.9
KPS				
100% (n=73)	2.07 ± 0.57	1.56 ±0.47	160.3 ± 52.6	120.2 ± 44.1
90% (n=111)	1.97 ± 0.46	1.46 ± 0.37	159.2 ± 44.7	118.8 ± 37.1
80% (n=22)	1.80 ± 0.45	1.23 ± 0.32	162.2 ± 52.9	110.3 ± 8.3
≤70% (n=1)	2.12 ± 0	1.41 ± 0	141.1 ± 0	94.2 ± 0
Missings (n=5)				

HCT-CI				
<3 (n=173, n=172)	1.99 ± 0.51	1.49 ± 0.42	159.9 ± 49.6	120.3 ± 41.2
≥3 (n=27, n=27)	1.98 ± 0.42	1.42 ± 0.37	158.5 ± 44.9	112.5 ± 35.5
Missings (n=12, n=13)				
T_Therapy				
<3 month´s (n=163, n=162)	2.00 ± 0.48	1.46 ± 0.39	160.5 ± 45.8	118.3 ± 38.4
3-6 month´s (n=38)	1.93 ± 0.55	1.49 ± 0.46	157.6 ± 58.1	121.6 ± 47.3
>6 month´s (n=14)	2.00 ± 0.63	1.45 ± 0.54	164.5 ± 58.7	122.6 ± 48.2
Missing (n=1, n=2)				
T_Diagnosis				
≤ 6 month´s (n=73, n=72)	1.96 ± 0.53	1.42 ± 0.42	154.4 ± 46.7	113.6 ± 40.4
≥ 7 month´s (n=137)	2.01 ± 0.49	1.50 ± 0.41	161.9 ± 49.2	120.8 ± 40.2
Missing (n=2, n=3)				
Physical activity (MET)				
<7.0 (n=143)	1.96 ± 0.48	1.44 ± 0.40	156.9 ± 47.7	116.1±39.8
≥7.0 (n=65)	2.01 ± 0.54	1.56 ± 0.44	166.3 ± 49.1	125.6±40.6
Missing (n=4)				
Hemoglobin last 3 month				
≤10 (g/dl) (n=67, n=66)	1.91 ± 0.50	1.39 ± 0.41	147.9 ± 47.5	108.8 ± 37.9
>10 (g/dl) (n=142)	2.03 ± 0.49	1.51 ± 0.46	165.6 ± 47.7	123.3 ± 40.3
Missing (n=3, n=4)				

Abbreviations: N=Newton metre; n = Number of Patients; BMI = body mass index; HCT-CI = Comorbidity Index by Sorror; KPS = Karnofsky Performance Status; alloHCT = allogeneic stem cell transplantation; AML = acute myeloic leukemia; ALL = acute lymphocytic leukemia; MM = multiple myeloma; CML = chronic myeloid leukemia; MPS = myeloproliferative syndrome; MDS = myelodysplastic syndrome. MVIC = maximal voluntary isometric contraction; MIPT = maximal isokinetic peak torque; MET = metabolic equivalent of task; T_Therapie = months between last therapy to allo-HCT; T_Diagnosis = months between last therapy to allo-HCT.

Discussion

Muscle function and performance in patients prior allo-HCT is considerably low. Our analysis in patients prior allo-HCT shows that two-third (66%) of the population have MVIC-values below the 50th percentile of the healthy reference group. Further, a considerable proportion of 84% for $MIPT_{Knee}$ and 83% for $MIPT_{Hip}$ are below the 50th percentile of the healthy reference group. Identified determinates for lower muscle strength were older age, lower BMI, being a women and having a higher comorbidity-index (HCT-CI). Compared to the healthy reference values in the percentile model, sub-group analyses showed that patients with younger age and male gender possess highest deviations when comparing to other gender/age subgroubs.

Generally, we found reductions strength parameter regardless of assessed muscle groups and testing procedure. Compared to other cancer populations where stationary dynamometry has been applied, MVIC values in knee extensors, as a representative value for the locomotor musculature and for daily functional tasks[23] were higher than those of pancreatic cancer patients[24] (mean $MVIC_{Knee}$ 159.7 Nm vs. 141.3 Nm respective 125.7 Nm). Similar results were obtained for the MVIC of the hip flexors. With regard to the MIPT values, the results are slightly higher[25]. When compared to breast cancer patients, our female subsample showed lower MVIC values of knee extensors, whereas the MIPT values are comparable or slightly higher depending on the treatment[15].

Several studies have examined muscle strength in hematologic patients, including allo-HCT candidates demonstrated impaired muscle strength and function[8, 10]. Yet the results demonstrate also substantial reductions in muscle strength. In a longitudinal designed study with lymphoma patients, it could be shown that strength capacity is also reduced even before treatment and further continues to decrease as treatment progresses[26]. In the context of allo-HCT, significant respiratory and skeletal muscle weakness is seen in patients after[7] and prior allo-HCT treatment[8]. Furthermore, in comparison with reference values, also significantly reduced muscle strength of the knee extensors were observed prior allo-HCT[27]. The current state of research seems to be very consistent with the results of cardiorespiratory fitness in allo-HCT candidates[4, 19, 28] and supports the present conclusions on muscle strength impairments and the global physical deconditioning of allo-HCT candidates.

Presumably, there are multicausal reasons for the reduced muscle strength: It is conceivable that various anti-cancer- treatments (e.g. doxorubicin) and their adverse side effects negatively impact muscle mass and function [29]. Although we were not able to significantly detect this association within our regression analysis, some variables (time since last chemotherapy treatment and number of carditoxic treatment) showed borderline results. A negative impact of chemotherapy treatment on muscle health, particularly in the lower extremities, has been reported elsewhere[30]. It can be assumed that the effects of various treatments and the diagnosis including their side effects in the patient's history may have contributed to the fatigue and related asthenia. This effect could be amplified by the fact that the related physical inactivity probably mainly leads to degeneration of the locomotor muscles [31, 32]. Associations between impairments in contractile strength, muscle function, muscle power, and cancer related fatigue with physical inactivity can be demonstrated [32]. The result is a kind of downward spiral[33] in which it becomes increasingly difficult to perform activities of daily living.

With regard to gender differences, not surprisingly, our regression model showed that the values of the female gender are significantly lower. However, the deviation from the reference values indicates that men have considerably lower muscle strength than women. This goes hand in hand with observations that sarcopenia was more prevalent in men and associated with higher fatigue values before allo-HCT [34]. This highlights the usually multi-factorial relationship between different patient specific variables such as patient's history (e.g. previous treatment) and the physical deconditioning. However, from a clinical perspective, other perspectives arise, which need to be considered. For example, sarcopenia (low muscle mass) is a major challenge, especially for older patients and will be further aggravated by systemic corticosteroid,

A further possible reason for lower MVIC and MIPT, could be related to hemodynamics respectively the reduced hemoglobin-levels. Kirkham and colleagues were able to show that muscle blood flow and O_2-extraction adapt to compensate for chemotherapy-induced hemoglobin reduction during exercise with small muscle mass, but are not sufficient to sustain exercise with large muscle mass[35]. However, this may be better detected in strength endurance tasks. In our analyses, hemoglobin was a marginally non-significant explaining factor of muscle strength for MIPT. This may reinforce the assumption that hemoglobin-level is primarily involved when large muscle groups (metabolic activity) are required, as we could identify it as an influencing factor of cardiorespiratory fitness[19]. On the other hand, the descriptive report reveals a remarkable deviation in muscle strength, in the group with lower hemoglobin values (hemoglobin value

MVIC -11.9% and hemoglobin value MIPT -13.3%). This suggests a possible influence and should be further considered in the risk assessment for low physical performance, also because anemia is known to be one of the most common hematologic abnormalities with its negative functional side effects[36].

The regression model did not show a significant influence of cardiotoxic treatment, as we could demonstrate on CRF[19]. Presumably, the nature of the testing procedure was not sufficient to identify deficits, as would be the case with longer-lasting and global exercise protocols[19, 28]. However, based on the state of the literature a negative impact on skeletal muscle of cardiotoxic therapies is conceivable[37] as well as glucocorticoid-induced myopathy[38, 39] and the general negative impact on muscle function of prior chemotherapies[40].

Significant influence was shown for higher age on lower muscle strength values. This is in line with observations, that muscle strength levels decreases with age. However, our results showed that the deviation from the healthy reference values was associated with patient age in that way, that younger patients were more affected by muscle strength loss than older patients. This is consistent with the findings that an increasing proportion of older patients are eligible for allo-HCT and not only the age but possibly also the muscle strength status is crucial[9]. With increasing age, an impact of comorbidities would also be conceivable[41]. Thus, at least, a significant impact of HCT-CI on $MVIC_{knee}$ has become apparent.

It has been shown that sarcopenia and the loss of muscle mass as well as low muscle strength is associated with risk for treatment-related complications and poor prognosis in patients undergoing allo-HCT treatment[9, 10, 42, 43]. Along with this, it has been observed that low knee extensor muscle strength values predict overall survival and non-relapse mortality after transplantation[10] and we are able to confirm essential impairments in lower extremity muscles. We are able to show that lower BMI values are predictive of lower muscle strength. This relationship is obvious on the one hand, but on the other hand there is an association between low pretransplant BMI and poor clinical outcome after allo-HCT[44].

There seems to be no clear consensus about the most probate screening tool or assessment method for physical performance prior allo-HCT as an essential contribution to the risk estimation of allo-HCT candidates. Probably a combination of divergent proofed assessment tools to assess muscle strength and cardiorespiratory fitness could provide a comprehensive and enlightening view of the global patients' physical performance, taking into account molecular and cellular dimensions to clarify the negative impact of given toxic treatments[5, 6].

These interactions between the individual physical functional system, treatment history and the disease itself must remain an integral part of further research. But based on these considerations, with the identification of influencing factors, the creation of risk profiles are conceivable, which could strengthen targeted exercise interventions. Initial approaches to exercise interventions before allo-HCT already exist, but the results also indicate that more specific conditions should be created for successful implementation in clinical practice[45].

Strengths of our investigation are the large sample and our applied gold standard muscle strength assessment procedures, limited by the factor of retrospective data collection obtained from available patient medical records. Furthermore, subgroup analyses of primary diagnosis

were not adequately powered and further studies are needed to provide specific estimation for high-risk patients of allo-HCT.

In conclusion, by applying gold standard assessment procedures we were able to quantify in a large sample that muscle strength values are remarkably reduced directly prior allo-HCT. We can contribute to the existing knowledge, that younger patients with male gender, lower hemoglobin-levels and comorbidity burden are particularly affected by muscle impairments. Our data supports the approach of integration of early exercise programs (prehabilitation) to prepare for allo-HCT. However, more research is needed on further (clinical) factors playing a role in risk stratification prior allo-HCT and that may be influenced by physical exercise.

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Conflicts of interest/Competing interests
The Authors declare no conflict of interest.

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

Consent to participate
All patients provide written informed consent.

Consent for publication
All patients provide written informed consent.

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5 MANUSCRIPT III

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Author Contributions
RK: study design, data collection, statistical analysis, writing the manuscript.
JF: contribution to statistical analysis.
ML: data collection, critical review of the manuscript.
AP, FS, HB, AW: data collection, critical review of the manuscript.
FR: contribution to the study design, critical review of the manuscript.
PD, TL: critical review of the manuscript.
JW: study design, critical review of the manuscript.
All authors contributed to the article and approved the submitted version.

Prehabilitative high-intensity interval training and resistance exercise in patients prior allogeneic stem cell transplantation

Rea Kuehl[1], Jule Feyer[1], Matthias Limbach[1], Antonia Pahl[2], Friederike Stoelzel[3], Heidrun Beck[4], Annika Wegner[5], Friederike Rosenberger[1,6], Peter Dreger[7], Thomas Luft[7], Joachim Wiskemann[1]

[1]Working Group Exercise Oncology, Division of Medical Oncology, National Center for Tumor Diseases (NCT) Heidelberg, Heidelberg, Germany
[2]Department of Hematology, Oncology and Stem Cell Transplantation, Medical Center -University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany
[3]Prevention Center of the National Center for Tumor Diseases Dresden (NCT/UCC), Dresden, Germany
[4]Department of Sports Medicine, University Center for Orthopedics, Trauma and Plastic Surgery, Dresden, Germany
[5]Medical Clinic II, Hematology-Oncology, University Clinic Frankfurt, University Cancer Center (UCT) Frankfurt, Frankfurt, Germany
[6]Division of Health Sciences, German University of Applied Sciences for Prevention and Health Management, Saarbrucken, Germany
[7]Department of Internal Medicine V, University Hospital Heidelberg, Heidelberg, Germany

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Abstract

Purpose Physical capacity prior allogeneic stem cell transplantation (allo-HCT) has been shown as a relevant prognostic factor for survival after transplant. Therefore, we evaluated feasibility and preliminary efficacy of a high-intensity interval training (HIIT) and moderate to high-intensity resistance exercise (RE) to increase physical capacity in patient's prior allo-HCT.

Methods In this multicentre single arm pilot study, a supervised exercise program was performed twice weekly for 4-12 weeks prior allo-HCT, depending on the individual time remaining. Outcomes were feasibility (recruitment, adherence, safety), physical capacity (cardiorespiratory fitness [VO2peak], muscle strength) and patient reported outcomes (physical functioning, fatigue).

Results Thirty patients were intended, 16 could be included, and 14 completed post intervention assessment (75% male, 55±11 years). The study was stopped early due to a low recruitment rate. Nine patients (64%) reached the initial minimum planned number of eight exercise sessions. Individual adherence was high with 92% for HIIT and 85% for RE. 87% of all performed exercise sessions were completed without complaints and VO2peak increased significantly from 20.4 to 23.4 ml/kg/min.

Conclusion The low recruitment rate suggests that initiation of the intervention concept immediately before allo-HCT is feasible only in a small number of patients. In particular, the

timeframe directly prior allo-HCT seems too short for exercise interventions, although the exercise program was designed to improve outcomes in a very short time frame. HIIT and RE were feasible, effective and well accepted by the included patients.

Clinical Trial registration: NCT03080792 (15/03/2017)

Keywords: exercise, prehabilitation, stem cell transplantation, cancer, cardiorespiratory fitness

Introduction

Allogeneic stem cell transplantation (allo-HCT) is an important treatment option for many hematological malignancies, e.g. leukemia or lymphoma. Although five-year survival rate is increasing due to advances in the management of complications e.g. graft versus host disease (GvHD) or infections [1, 2], physical capacity after allo-HCT remains low [3-5], and patients suffer from reduced quality of life (QOL) [6, 7]. Almost half of the patients show moderate to severe impairments in exercise capacity one year after allo-HCT resulting in disability, fatigue und reduced QOL [4].

Evidence suggests that exercise interventions in patients with haematological cancer are safe and beneficial. Positive effects range from improved physical capacity to psychosocial effects, resulting in enhanced QOL [8-10].

However, patients experience significant reductions in physical capacity [11-15] already prior allo-HCT. First observational studies demonstrate that objectively assessed cardio-respiratory fitness (CRF) through a cardiopulmonary exercise test at exhaustion (CPET, with VO2peak outcome measure) was a significant predictor for overall survival and non-relapse mortality, [16, 17]. Retrospective data support these findings [18].

Therefore, it seems to be important to implement exercise interventions prior allo-HCT to achieve a higher level of physical function prior treatment. This concept of prehabilitation has been already examined in cancer pre-surgical settings and proved to be safe and feasible [20-22]. However, only one small pilot study proved the concept of prehabilitation in allo-HCT. The intervention (individually tailored home-based exercise) was safe and feasible and after at least six weeks of intervention, patients significantly improve their CRF [23].

In summary, the pre-transplant period seems to be an important and insufficiently investigated research area with the prospect to improve clinical outcomes and prognosis. However, the time frame from scheduling of planned allo-HCT to admission is usually relatively short. It thus seems pivotal to choose an exercise intervention that is able to improve physical capacity in a very short time such as high-intensity interval training (HIIT). HIIT is characterized by relatively short bouts of high-intensity workloads interspersed by periods of low-intensity workloads for recovery. Hereby, the total accumulated time of vigorous exercise is higher than what could be achieved during continuous exercise (usually moderate intensity) [24]. A recent meta-analysis of HIIT-effects in the prehabilitation of cancer treatment include seven RCTs and show a significant improvement in CRF and positive effects for health-related outcomes [25].

Therefore, this pilot-study evaluates safety and feasibility of a combined moderate-to HIIT and RE program in patients with haematological cancer prior allo-HCT. Preliminary efficacy data on CRF, muscle strength, QOL and fatigue were also assessed.

Methods

The study was a multicentre, prospective, single-arm study to investigate safety and feasibility of moderate to high-intensity HIIT and RE in patients with haematological cancer prior allo-HCT. The study (PRESENT-P trial [Pre-Exercise for allogeneic stem cell transplant patients: a pilot-study]) was conducted at the National Center for Tumor Diseases (NCT) Heidelberg and University Hospital Heidelberg, National Center for Tumor Diseases Dresden (NCT/UCC), the Department of Hematology, Oncology, and Stem Cell Transplantation University Medical Center Freiburg and the University Center for Tumor Diseases (UCT) Frankfurt, Germany, between November 2016 and February 2019. The study was approved by the ethics committee (leading committee) of the University Hospital Heidelberg and validated by the local committees of the clinical partners and is registered at ClinicalTrials.gov (NCT03080792; 15/03/2017). All participants provided written informed consent prior initiating any study activity.

Patients were eligible to participate when they met the following inclusion criteria: hematological cancer with allo-HCT scheduled within the next four to 12 weeks, ≥ 18 years of age, sufficient German language skills, willing/ able to train at the provided exercise facilities twice weekly. Exclusion criteria were: heart insufficiency >NYHA III or uncertain arrhythmia, uncontrolled hypertension, severe renal dysfunction (GFR < 30%, Creatinine >3mg/dl), insufficient hematological capacity (either haemoglobin value below 8 g/dl or thrombocytes below 30.000/ μL, reduced standing or walking ability, further comorbidities that preclude participation in the exercise program, and engaging in systematic intense exercise training (at least 1h twice weekly). Patients were screened and recruited 4-12 weeks prior admission for allo-HCT. When allo-HCT was scheduled, patients were informed about the study by their treating hematologist. Further information they received from the study personnel at each center.

Intervention

The prehabilitation intervention comprised of individually tailored supervised exercise sessions twice weekly for 4 to 12 weeks. The total duration of the individual intervention length depended on the final scheduling of transplantation. The exercise program consisted of a supervised HIIT on a bicycle ergometer and RE.

The HIIT-protocol was individualized based on the peak power output (PPO) achieved in the cardiopulmonary exercise test (CPET) prior intervention (t0) and comprised eight one-minute high-intensity bouts at 90-100% PPO, interrupted by one-minute rest periods at 50% PPO. Each session started with a 5-10 minute warm up at 50% PPO and ended with a 5-minute cool-down at 50% PPO. The first two exercise sessions were familiarization sessions at slightly lower intensities of 70% PPO. The selection of exercise intensities was based on own findings where we defined

exercise intensities in a sample of patients prior allo-HCT [27] and developed based on findings in patients with chronic heart failure [28].

HIIT was followed by a 30 minute moderate to intense RE program that include four to six exercises targeting the whole body (legs, arms, shoulders, back, and chest) at resistance training machines or free weights. RE was performed at an intensity of 12 repetition maximum, based on a one repetition maximum test (1-RM, only for resistance training machines). The 1-RM was applied after one familiarization session according to approved methods [29]. Two sets of each exercise were performed (2x12 repetitions) at 60-80% of 1 RM.

All exercise sessions were supervised by exercise specialists and performed at one of the recruiting centres or at certified exercise facilities provided by the OnkoAktiv network. The OnkoActive network is a German network with which we link health-oriented exercise facilities to enable training close to patients home. The exercise program complies with the American College of Sports Medicine (ACSM) exercise guidelines for cancer survivors [30]. When patients were not able to exercise at this high intensity, exercise intensity was reduced to a tolerable intensity (Rating of perceived exertion (RPE) <18, [26]). Exercise was contraindicated during fever and acute infections, when thrombocytes dropped below 15.000/µl and when haemoglobin values were <8g/dl. Exercise intensity was reduced to 60% PPO when thrombocytes dropped under 20.000/µl and for RE to 40% 1 RM.

Measures

All participants underwent assessment prior intervention (t0) and post intervention/ prior admission for allo-HCT (t1). CRF was measured via CPET on an electronically braked cycle ergometer (Ergoselect 100; Ergoline, Bitz, Germany). We measured peak oxygen uptake (VO2peak) and PPO for exercise prescription. During the graded exercise test (starting with 2-min unloaded warm-up, the load was increased by 10 watt every minute, starting at 20 watt) respiratory gas exchange was measured continuously using a breath-by-breath system (Ergostik; Geratherm Respiratory, Bad Kissingen, Germany). Gas exchange data and HR were stationary time averaged over 30s. VO2peak and HRmax were considered as the highest 30-s average value during or immediately post exercise. For safety reasons, a 12-lead electrocardiogram (ECG) was recorded continuously. Patients were encouraged to spend maximal effort until voluntary exhaustion.

Additionally, all patients underwent a 6-min walk test according to published guidelines [31]. For isometric muscle strength assessment, hand grip strength (HGS) was assessed on both sides using JAMAR handgrip dynamometer (Patterson Medical, Warrenville, IL, USA). The test was performed in a sitting position with the elbow attached to the trunk and elbow angle of 90º. The best out of three attempts for both sides was analysed. Additionally, maximum voluntary isometric contraction (MVIC) was measured with IsoMed 2000-system (D&R Ferstl GmbH, Hemau, Germany) for knee extension, elbow flexion and hip flexion at both sides.

QOL was assessed with the validated questionnaire of the European Organisation for Research and Treatment of Cancer (EORTC QOL-C30) [32] and fatigue with the Multidimensional Fatigue

Inventory (MFI) [33]. Sociodemographic and medical information were partly obtained from medical records and partly self-reported. Shortly before and directly after each exercise sessions patients reported on actual symptoms, based on the Edmonton Symptom Assessment Scale (ESAS, VAS 0-10) [34] and provide a general feedback of the exercise session. The satisfaction of the patients with the intervention was assessed at the end of the intervention on a visual analogue scale (VAS 1-7).

Statistical methods

Since PRESENT-P is a pilot-study that will provide information for a larger confirmatory RCT, no power calculation has been conducted and data were mainly of descriptive nature. We planned to recruit n=30 patients in four centres. Due to the short time period between indication of allo-HCT and the start of treatment, our feasibility goal was to enable all included patients to perform at least eight prehabilitative exercise sessions before admission for transplantation. Further, we calculated exercise adherence for each patient individually, based on the individual number of available weeks. For this feasibility outcome, we considered a rate of 75% (at least eight exercise sessions possible and adherence to the sessions) as adequate. Regarding safety considerations, we reported on exercise related side effects (e.g. pain, bleeding signs). For preliminary efficacy, we did pre-post comparisons using Wilcoxon rank-sum test, Cohen's d for VO2peak and present individual responses. All analyses were conducted in SPSS statistical software package (V26).

Results

During the recruitment period between 11/2016 until 02/2019, 16 patients were included (n= 10 Heidelberg; n=3 Dresden; n=2 Freiburg, n=1 Frankfurt). Enrolment stopped before the anticipated number of participants was reached because of low recruitment rate due to various reasons. Two patients dropped out (n= 1 allo-HCT postponed, n=1 reason unknown). In total, 16 patients underwent baseline testing, n=14 patients post-intervention testing (attrition rate 87.5%). Patient characteristics are presented in Table 1.

Table 1: Sociodemographic and medical data (n=16)

	n		
Gender			
Male	12	75%	
Female	4	25%	
Age (mean, SD)	55.3	10.8	Range: 28-69
BMI (mean, SD)	25.0	5.4	Range: 18.6-42.8
Family status			
Living with partner(s)	11	69%	
Living alone	4	25%	
Missing	1	6%	
Education			
Low	4	25%	
Medium	2	13%	
High	9	56%	

Missing	1	6%	
Employment			
Yes	5	31%	
Up till diagnosis	8	50%	
Retired	1	6%	
Missing	2	13%	
Diagnosis			
MDS	5	31%	
Hodgkin's/Non-Hodgkin's Lymphoma	5	31%	
ALL	3	19%	
AML	2	13%	
AA	1	6%	
Time since Diagnosis in months (mean, SD)	44.7	58.3	Range: 1-183
First year after diagnosis	7	44%	
Therapy			
No	5	31%	
Chemotherapy	9	56%	
Radiation	3	19%	
Immunotherapy	4	25%	
Missing	1	6%	
Hemoglobin level in g/dl (mean, SD)	13.2	9.99	Range: 6.6-13.2
Missing	1		
Thrombocytes in /µl (mean, SD)	131	122	Range: 25-493
Missing	1		
Physical activity in the last 12 month before diagnosis (e.g. brisk walking, exercise activities)			
Yes	8	50%	
No	7	44%	
Missing	1	6%	
Physical activity in the last 4 weeks (e.g. brisk walking, exercise activities)			
Yes	4	25%	
No	7	44%	
Missing	1	6%	

Feasibility, Adherence and Safety

In total, 133 exercise sessions were performed. Intervention length was 5.1 weeks (median 4.4, ranging 1.4-11.6 weeks). Nine patients (64.3%) reached the initial minimum planned number of eight exercise sessions. The mean number of completed exercise sessions was 9.5 (median 8.5, range 3-19). Figure 1 displays the individual adherence to HIIT and RE. Adherence to HIIT was 92% with overall mean interval per exercise of 7.4 from 8 intervals. Adherence to RE was 85.4% with overall mean of 11.7 repetitions (from 12 repetitions per 2 sets).

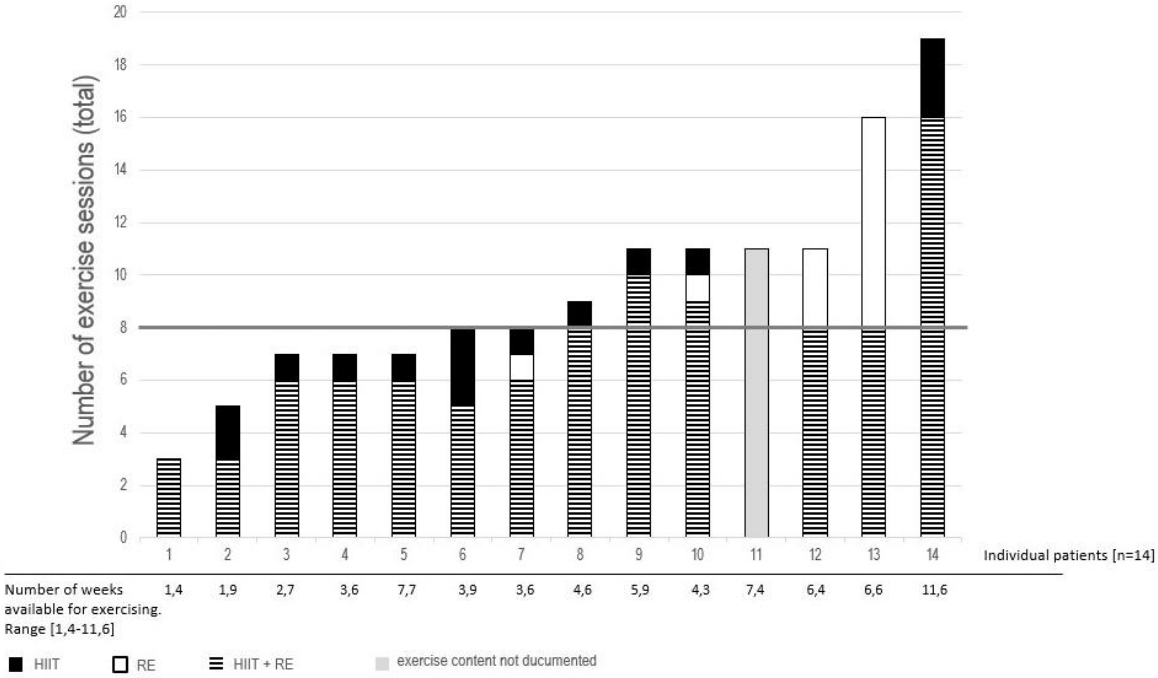

Figure 1: Exercise adherence. Individual amount of exercise sessions categorized in HIIT and RE (133 sessions in total). HIIT, high intensity interval training; RE, resistance exercise. [Example: Patient no 5 exercised 7 sessions in total, 6 sessions were combined sessions (HIIT + RE) and one session only HIIT].

We received direct feedback of 128 exercise sessions. One-hundred-twelve exercise sessions (87.5%) were without complaints. Session with complaints include the following: four (3.1%) sessions had a premature ending (2x during HIIT because of exhaustion and palpitations; 2x during RE because of shoulder pain and lack of energy/weakness; in five (3.9%) sessions patients were unable to perform certain exercises (e.g. reduced intensity or termination of HIIT, termination of certain RE exercises; in seven (5.5%) sessions patients felt discomfort (e.g. 2x vertigo directly after strain, 2x exhaustion). At the beginning of 8 sessions (6.3%) patients reported on pain (e.g. muscle soreness, knee pain) associated with the last training session. Further reported complaints like dyspnoea, nausea, infections and bleeding signs were not related to exercise. No adverse events were reported. One-hundred-twelve (87.5%) sessions were rated with "just the right intensity", eight sessions (6.3%) were rated with "overstraining" (5x same patient) and seven sessions (5.5%) were rated with "underdemanding". Enjoyment after each session was rated with 6.4 (MW, median 7) out of 7 points.

After intervention program, likeability (6.64), helpfulness (6.79), enjoyment (6.64), and recommendation to others (6.79) were rated on average with 6.65 out of 7 points. Patients rated the positive effect on the individual physical condition with 6.2 and the positive effect for the psychological effect with 5.4 out of 7.

Preliminary efficacy

After the intervention program, VO2peak increased significantly from 20.4 to 23.4 ml/kg/min (median improvement 2.15 ml/kg/min, z=-2.34, p=0.019, CI 95% 0.67; 5.35, d=1.6). The individual changes of VO2peak in ml/kg/min are presented in figure 2, including individual baseline level of

all patients. PPO increased significantly from 117 to 131.2 W (median improvement 15 W, z=-2,56, p=0.010, CI 95% 5.04; 23.53).

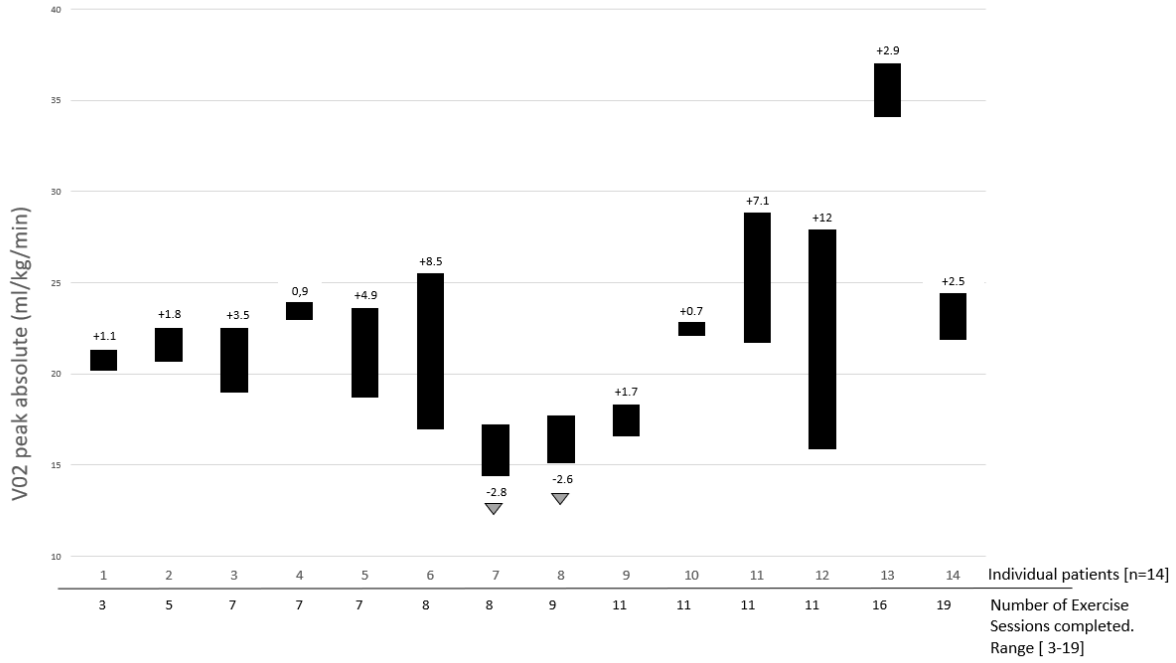

Figure 2. Individual change of VO2peak including individual baseline level and individual increase in ml/kg/min.

Completed distance in the 6-min walk test increased significantly from 558.8 meters to 608.6 meters (median improvement 30.5 meters, z=-2.03, p=0.043). HGS (n=9) increased significantly from 37.8 to 39.6 kg at the dominant side (median improvement 2 kg, z=-2.06, p=0.040) and from 35.4 to 39.5kg at the non-dominant side (median improvement 2 kg, z=-2.38, p=0.018). The MVIC test (n=11) showed no significant changes in muscle strength of knee-extension (change of the dominant side: +11.25 Nm), elbow-flexion (change of the dominant side: +2.13 Nm) and the hip-flexion (change of the dominant side: -14.00 Nm) at the dominant and non-dominant side.

Table 2 displays changes in patient reported outcomes (PROs). Significant improvements could be shown in physical functioning, role functioning, emotional functioning, fatigue and dyspnoea. Results of the MFI show a significant reduction of physical fatigue and reduced activity after intervention period.

Table 2: Effects of 4-12 week exercise intervention on Quality of Life (EORTC-C30) and Fatigue (MFI, different domains) (n=14)

	T0	**T1**		
	MW(SD)	MW(SD)	Mean Change (CI 95%)	p*
EORTC-C30				
Global QOL	56.25 (21.65)	64.74 (14.89)	8.33 (-2.73; 19.39)	0.107
Physical functioning	75.90 (15.04)	87.18 (11.69)	11.28 (2.83; 19.73)	**0.010**
Role functioning	52.56 (33.23)	71.79 (24.89)	34.62 (15.30; 53.93)	**0.041**
Emotional functioning	47.44 (25.54)	66.03 (20.26)	18.59 (10.59; 26.59)	**0.004**

Cognitive functioning	64.74 (14.89)	71.79 (18.49)	7.69 (-3.65; 19.04)	0.161
Social functioning	56.41 (30.08)	64.10 (27.93)	7.69 (-4.38; 19.76)	0.193
Fatigue	53.85 (19.27)	32.91 (17.34)	-20.94 (-33.59; -8.29)	**0.007**
Nausea/vomiting	3.85 (7.31)	1.28 (4.62)	-2.56 (-6.35; 1.22)	0.157
Pain	23.08 (26.82)	19.23 (19.06)	-3.84 (-21.37; 13.67)	0.589
Dyspnoea	35.90 (31.80)	12.82 (16.88)	-23.08 (-42.16; -3.40)	**0.024**
Insomnia	33.33 (36.00)	23.08 (25.04)	-10.26 (-25.39; 4.87)	0.157
Appetite loss	23.08 (25.04)	5.13 (12.52)	-17.95 (-35.62; -0.28)	0.053
Constipation	12.82 (28.99)	7.69 (14.62)	-5.13 (-16.30; 6.05)	0.317
Diarrhoea	15.38 (25.87)	7.69 (19.97)	-7.69 (-22.30; 6.91)	0.257
Financial difficulties	25.64 (24.17)	25.64 (30.89)	0.00 (-11.63; 11.63)	1.000
MFI (n=13)				
General fatigue	13.31 (2.63)	12.00 (3.14)	-1.31 (-3.01; 0.39)	0.179
Physical fatigue	13.54 (4.58)	10.77 (3.59)	-2.77 (-5.15; -0.39)	**0.030**
Reduced activity	12.54 (3.38)	9.85 (3.11)	-2.69 (-4.85; -0.54)	**0.013**
Reduced motivation	8.31 (2.32)	7.62 (2.79)	-0.69 (-2.54; 1.16)	0.477
Mental fatigue	11.08 (4.82)	10.46 (4.24)	-0.62 (-2.26; 1.03)	0.453

To assess a *single session effect* we compared the results from the ESAS Scale from directly prior to directly after every session. Patients had a significant reduction of pain (z=-2.19, p=0.028), anxiety (z=-3.07, p=0.002) and general well-being (z=-2.82, p=.0.005 [lower values belongs to better general well-being]) directly after the exercise sessions. For nausea, depression, drowsiness, appetite and dyspnoea no changes could be found.

Discussion

In this pilot-trial, we investigated a supervised HIIT and RE exercise program in patients prior allo-HCT with the aim to improve CRF and muscle strength in a very short timeframe. Results show that our prehabilitation exercise program was feasible, safe, effective, and well accepted by participating patients. However, due to low recruitment rate, the study was stopped before we reached the anticipated number of n=30 patients.

The initial minimum planned number of eight exercise sessions prior allo-HCT was achieved by nine patients (64.3%). However, only 5.1 (range 1.4-11.6) weeks of training were possible due to scheduling for allo-HCT. Hence, it seems that adherence to exercise was not problematic (adherence depending on individual intervention length was 92% for HIIT and 85.4% for RE), but timing of the intervention, respectively the short time-period available after scheduling for allo-HCT.

All study centres had problems recruiting the patients within our planned recruitment period due to the tight time frame of the patients directly prior allo-HCT. For example, in Heidelberg (Germany) the recruiting study personnel attended the weekly transplant board to screen for eligible patients. Almost all patients received their schedule for allo-HCT only 2 weeks in advanced and were therefore not eligible for this study (inclusion criteria: 4-12 weeks prior planned admission/conditioning for allo-HCT). Main reasons for the short-term planning were the changing clinical status of patients and donor availability. However, this is an organisational

problem which cannot be changed by the given procedures in the participating transplant clinics. Further challenges included personal resources, e.g. lack of work force and no capacity by physicians to screen for eligible patients. Therefore, recruitment was very challenging, and for this prehabilitation study concept is was not feasible. We thus stopped recruitment before we reached the anticipated number of n=30 patients due to the longer recruitment period than anticipated and lack of manpower. Thus, a better collaboration between clinicians and exercise professionals should be sought for future projects.

Another, recently published pilot RCT in patients prior allo-HCT from the US faced similar problems (including insufficient time for exercise before allo-HCT) and the study was stopped because of low recruitment rate as well [35]. Given these similar implementation barriers of studies in this setting it needs to be questioned, whether the chosen approaches fit with the clinical patient flow as well as with the demands of allo-HCT patients and their medical treaters. Scientifically, it seems to be indisputable that patients should be at their individual best physical constitution and function level, when they are entering the transplant process. If the medical team is also convinced by this evidence, there is a need to offer an extend time frame to enrol patients in a prehabilitation program prior allo-HCT which requires a modified transplant preparation procedure. Additionally, by incorporating exercise prehabilitation as a routine procedure in the allo-HCT preparation this might led to improved transplant eligibility. Facing the older and partly multimorbid/frail–patient populations scheduled for allo-HCT, future comprehensive transplant programs will not be able to ignore the potential of prehabilitation measures when preparing the patients for this challenging treatment procedure.

Despite problems in recruitment, our prehabilitation concept was safe, feasible and effective for the included patients. Our attrition rate was 87.5% and adherence was with 92% to HIIT and 85.4% to RE relatively high in comparison to two pilot studies prior autologous and allo-HCT [23, 36] and to our RCTs in allo-HCT during and after transplantation [37, 38]. In comparison to the concept of Wood et al. our intervention program was supervised, more standardised in terms of the exercise contend (free chosen activity vs HIIT protocol on a bicycle ergometer of 8x 1 min high-intensity at 90-100% PPO) and included moderate to high-intensity resistance exercise [35]. A recent review of HIIT in cancer patients reported an adherence between 71.2% and 95.6% [39]. We think that the combination of short intervention period, supervised training (including appointments with the exercise facility) and diverse exercise content have led to the high adherence rate in our study. The very good feedback on likeability, helpfulness and enjoyment underline the feasibility of the exercise program. However, for future studies it would be helpful to have additionally an exercise facility integrated in the transplant unit so that patients could also train directly in the clinic. Particularly in the view of the limited time available, this would make the implementation of exercise much easier.

In our study, only 11 sessions (6,3%) were rated with “overstraining” indicating that our demanding high to moderate intensity exercise program was feasible and acceptable. However, four exercise sessions had a premature ending because of exhaustion and lack of energy and in five sessions, the intensity needed to be reduced or single exercises (RE) needed to be terminated. Since patient’s prior allo-HCT have already limitations in physical capacity caused by previous treatments [14] and the clinical status can vary, a good monitoring of training load during every exercise session is mandatory.

Evidence showed that the objectively measured physical capacity prior allo-HCT has an impact on outcomes, such as prognosis and symptom severity [11, 15-18]. Therefore, it is of high clinical importance to increase CRF and functionality already prior allo-HCT. Furthermore, it is assumed that building up physiological reserve will lead to better treatment tolerance due to higher level of physiologic function throughout treatment and may mitigate further decline after allo-HCT due to complications e.g. GvHD. GvHD after allo-HCT is associated with a further decline in functional performance and reduced QOL [40]. Despite the short intervention period of 5.5 weeks available and 9.5 exercise sessions performed, we observe significant effects on physical capacity measures.

VO2peak increased significantly from 20.4 to 23.4 ml/kg/min and PPO increased significantly from 117 to 131 W. This VO2 peak improvement correspond to a very large effect (Choen's d = 1.6). However, these results are in line with the results of another pilot study prior transplantation, where 3.7ml/kg/min of VO2peak improvement in the allo-HCT patients could be observed [23]. It could be shown that a VO2peak decrease of 1ml/kg/min was associated with higher mortality rates after allo-HCT (HR 1.13) [17]. Interestingly, there was a large variance in the initial performance level and the response of the patients seemed not to depend on number of exercise sessions performed or initial value. However, in 5 patients the VO2peak value prior allo-HCT lay below the threshold of 18ml/kg/min, which was proposed to be a threshold for physically independence in older adults [41]. Though, after intervention only 2 patients lay below the threshold. Interestingly, these 2 patients were the ones who did not improve their VO2peak but deteriorated. We can speculate, if for those two patients the intervention program did not fit. However, another patient that started on a very low level could clearly increase his VO2peak, but had more exercise sessions available. Therefore, it could be that patients with a very low performance need more sessions to achieve a clear training effect on VO2peak.

We can speculate on further influencing factors that may play a role for the response. For example, clinical factors, e.g. the pre-treatment including cardiotoxic argents, blood counts (e.g. hemoglobin value) may play a role here [42]. In or previous work we performed an analysis on influencing clinical factors on the VO2peak prior allo-HCT [14], however, it would be interesting to perform an subgroup analysis on the influence of different factors on the exercise response prior allo-HCT in future studies.

The 6-min walking distance improved significantly by 30.5 meters which is comparable to other studies in this setting [23]. In clinical populations, the minimum clinically important difference is defined as 14.0-30.5 meters [43]. In allo-HCT it could be shown that each 100 meter decrease was associated with a higher risk of mortality (HR 2.98) [17]. In our previous RCT we demonstrated that a higher baseline fitness (meters in 6 min walking test) were associated with lower total mortality rates in a multivariate model [18]. This study could also demonstrate that a partly supervised exercise program may reduce mortality rates after allo-HCT [18].

Since not only a great CRF seems to improve outcome after allo-HCT, but also sarcopenia was associated with higher non-relapse mortality and shorter overall survival after allo-HCT [15, 44], we included RE in our exercise intervention. Our previous RCTs in patients during and after allo-HCT demonstrated the feasibility and effectiveness of combined interventions [18, 37, 38]. A recent study revealed the HGS as a significant predictor for non-relapse mortality (HR 2.56) [45].

Our results showed a significant improvement of HGS of about 2kg, indicating a positive effect of our RE on HGS.

So far, very few prehabilitation studies focused on PROs. However, not only physical capacity, but also a better QOL prior allo-HCT was associated with reduced risk of mortality [46]. A reduced symptom severity, e.g. reduced fatigue and physical functioning will lead to better general QOL throughout treatment. Our intervention had a significant positive impact on physical functioning, role functioning, emotional functioning, fatigue (physical fatigue, reduced activity) and dyspnoea. Previous interventions with moderate intensity training during or after allo-HCT demonstrated the positive effect of exercise on various PROs [9].

Strengths of our study included a sound intervention concept, including highly standardised HIIT and RE and individualized exercise prescription using percentages from the individual maximal capacity for both, HIIT and RE. Additionally, a highly standardised measurement protocol was applied, including gold-standard methods to assess CRF. Furthermore, our exercise intervention was supervised to ensure a safe completion and good adherence to the exercise protocol. Our study also used a multicentre approach to gain results regarding recruiting structures from different study centres. However, our study has several limitations and our findings must be interpreted cautiously. First of all, we had a small sample size due to a low recruitment rate and most of the participants were being recruited in one study centre (Heidelberg). Furthermore, our sample seems not to fully represent patient's diversity according disease distribution prior allo-HCT because most participants were diagnosed with MDS or Lymphoma. Normally, AML is the most frequently diagnosis for allo-HCT. Finally, this was a single arm pilot study with a small sample size and larger randomized studies are necessary to confirm our results.

Conclusion

Our study showed that HIIT and high-to moderate RE is feasible for patients prior allo-HCT and may improve CRF and PROs in a very short timeframe. This is clinically highly relevant since a higher physical capacity prior allo-HCT may improve symptoms and survival. However, recruitment rates were much too low and recruitment needed to be terminated. Therefore, we conclude that the time-point in the weeks prior allo-HCT need to be expanded and include also patients with planned allo-HCT but without further scheduling. Especially patients with high-risk profiles and low physical capacity should be offered a structured and individually tailored exercise program as supportive care option to enhance physical capacity/ CRF and ultimately improve outcomes such as survival.

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Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

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6 General Discussion

The first part of the thesis attempts to better define the performance status of patients prior to allo-HCT and to provide targeted-recommendations for exercise therapy. This results from the fact that the physical performance parameters of CRF and muscle strength prove to be increasingly relevant for the treatment process and patients prognosis (Manuscript I and II). As a consequence, exercise therapy programs need to be developed with the aim of improving and raising the patient's status already before the start of treatment. This could enable a positive change in the risk management of the patients. The second part of the thesis tries to find answers to the question whether an intervention by exercise training in the short time directly prior to allo-HCT is feasible and whether patients benefit in parameters of physical performance (Manuscript III).

6.1 Summary of main findings

We were able to show, based on the largest population to our knowledge to date in the setting of allo-HCT using gold standard measurement methods, that patients are considerably physically deconditioned even before the beginning of allo-HCT. CRF values and the muscle strength are considerably reduced.

Based on 194 patients who underwent CPET immediately prior (mean 2.9 days) to allo-HCT, it could be shown that patient subgroups of older age, female gender, with low hemoglobin levels (AUC, are under the curve), who received cardiotoxic treatment prior to allo-HCT and have low physical activity behavior, have a risk for lower CRF. Overall, significant deviations of CRF from gender- and age-matched data of a healthy reference population were demonstrated (-27.5%; $p<0.05$). Considering these VO_{2peak} reference values by Koch et al[178], men as well as patients of younger age have a higher risk for lower CRF. Furthermore, higher BMI and lower physical activity were significant predictors of low CRF in the regression models (see Manuscript I).

Interesting parallels can be drawn to muscle strength prior allo-HCT. Our investigation with 212 patients (Manuscript II) also reveals considerable deviations from healthy reference values, which are also age- and gender related. It is striking that again patients with a younger age and male gender have higher deviations from the norm values. The regression

models, on the other hand, showed that older age, lower BMI, and women have a higher risk of lower strength values, both for $MVIC_{Knee}$ and $MIPT_{Knee}$. Furthermore, HCT-CI seems to have a significant influence on $MIPT_{Knee}$. The descriptive report reveals especially lower values for the subgroups with a lower active device behavior and a lower Hb-level in the last 3 months. This is valid for both MVIC and MIPT. In addition, low hemoglobin values show a trend towards statistical significance for $MIPT_{Knee}$ ($p=.052$) for correspondingly long-lasting movements. Overall, there seems to be a multifactorial influence between different patient-specific variables and treatment history on physical deconditioning. Lower extremity muscle strength appears to be well qualified to represent reduced physical functioning. These results are consistent with those from Manuscript I (reduced CRF). Noticeable limitations for activities of daily living are to be expected.
The results of the first two studies (Manuscript I and II) suggest and further confirm the assumption that exercise training is induced even prior allo-HCT. Furthermore, we were able to determine potentially influencing factors on patients' physical performance, allowing us to give statements about a vulnerable group of patients.
First of all, due to the weak study situation regarding pretraining, especially in the field of allo-HCT, it must be examined whether and how exercise interventions are successful.

Our single-arm multicenter pilot study has shown that training using HIIT and a high-to-moderate intensity RE is feasible for patients even directly before allo-HCT and, moreover, can improve physical performance as well as PROs. This is of very high clinical relevance, not only because this was possible in a very short period of time, but also because of the prognostic significance of better physical performance. Based on 14 patients who completed the study, significant effects on CRF (VO_{2peak} 20.4 to 23.4 ml/kg/min) and 6MWT performance were obtained. Significant results on muscle strength were only generated for hand grip strength (+2kg), whereas MVIC values depicted a positive trend. Further, we could highlight that our exercise intervention had a beneficial and significant influence on PRO´s: physical functioning, role functioning, emotional functioning, fatigue and dyspnea. Although the concept of the exercise intervention proved feasible, as represented by the individual adherence (92% for HIIT and 85% for RE 87% of all performed exercise sessions were completed without complaints) the study had to be cancelled due to low recruitment rates, which questioned the method of implementation, but the exercise training specific content is promising.

6.2 Discussion

This chapter relates the obtained findings and addresses existing limitations. It is divided into *the parameters of CRF and muscle strength, low physical performance and the estimation of the risk, exercise in the time prior allo-HCT, chances of pretraining, recruitment and feasibility* and *conclusions for exercise intervention profiles.*

THE PARAMETERS OF CRF AND MUSCLE STRENGTH

The findings of Manuscript I and II, based from data collected as part of the PETRA study, presented in the cumulative dissertation at hand, are in line with the current state of literature, regarding the fact that patients show limited physical performance even before allo-HCT[95, 102, 132, 135, 190]. These results are valid for both CRF and muscle strength. On the one hand, it could be shown that CRF and muscle strength values deviate considerably from a healthy age- and gender matched population, and on the other hand, potential predictors of low CRF and muscle strength have been identified (Manuscript I and II). Furthermore, for a valid comparison of the physical performance, however, values with the same measurement methods should also be involved. The comparisons of the CRF reveal a higher deviation of reference values with pancreas cancer[182], whereas breast cancer patients of similar age show lower values[181]. In terms of muscle strength, slightly higher values can be detected in our sample than in pancreatic cancer patients[191]. In contrast, our female subsample had lower knee extension MVIC values and slightly higher or comparable MIPT values to breast cancer patients[186].

In conclusion, due to the sample size and the high quality assessments of our study, previous data in the literature could be substantiated. Although the physical condition of patients before allo-HCT is a substantial topic, it is still understudied.

LOW PHYSICAL PERFORMANCE AND THE ESTIMATION OF THE RISK

As outlined in Chapter 1.5 (Risk estimation and selection of appropriate patients for allo-HCT) and Chapter 1.6.1-1.6.2 (State of the Art Impairments CRF and muscle strength), the risk scores are well justified and can help in the appropriate risk classification of allo-HCT candidates. Different results are available, which try to compare the risk estimation based on the risk-score system (e.g. HCT-CI) and the VO_{2peak} values. In one study, VO_{2peak} was not shown to improve prognostic prediction when compared with commonly used scores. For most scores, no association was found between VO_{2peak} and OS or NRM[183]. Others, however, show that combinations of the VO_{2peak} and the HCT-CI possess a predictive value[192]. Overall, there is a need for further investigation in this area, but this does not negate the importance

of prognostic- systems. Certainly, the classical assessments (LVEF, FEV1 and DLCO) continue to exist. Although it is discussed that the physical functional systems can possibly be better represented under exercise conditions and thus measurements such as CPET achieve a very high relevance[102, 193]. Also, sarcopenia is thought to increase the risk for OS and higher NRM after allo-HCT[138] as well as a close association between muscle strength and sarcopenia seems to exist[135]. In this relationship, and in the context of risk stratification, it appears to be possible to illustrate that muscle strength rather than muscle mass has been shown to be the most important component[96, 194]. In this context, we found that BMI emerged as a significant predictor of reduced muscle strength. This is not surprising, since people with lower body weight are likely to have less strength. However, it should not be ignored that a low pretransplant BMI may be associated with worse clinical outcomes after allo-HCT[139]. For this purpose, further analyses are certainly useful to investigate not only BMI but also body composition in more detail.

Referring to the impairments of CRF (Manuscript I) and muscle strength (Manuscript II), respectively, and the associated risk stratification as well as prognosis and improvement of clinical outcomes (Chapter 1.6), it can be deduced that the parameters of physical performance should be built up prior to allo-HCT.

EXERCISE IN THE TIME PRIOR ALLO-HCT

There is already knowledge that physical exercise is possible during treatment with chemotherapy[195], also diagnosis-specific findings are available that can potentially take place in the time before allo-HCT. Such as an exercise intervention in AL- patients during induction chemotherapy not only leads to an increase in maximal strength, but also endurance capacity (VT) could be improved despite an intensive treatment[196]. Comparable results were obtained in a study of AML-patients, also treated with induction chemotherapy[197]. It is important that patients have access to intervention concepts, because preliminary results suggest that the higher the values of CRF as well as muscle strength before transplantation, the higher they are afterwards. This also reinforces the rationale for pretraining[198]. Physical training can be seen as a chance to compensate for therapy-related impairments, but it remains to be seen how exactly the benefit will turn out. In the future, attention might be paid to specific groups of patients for which an exercise intervention potentially better can be planned in consideration to their time prior to allo-HCT. To date, there are no clear findings and studies often include different entities.

CHANCES OF PRETRAINING

As the data from the PRESENT-P study show, positive effects on CRF and muscle strength (Manuscript III) are possible with intensive training. These results are identical when compared with the current literature. Thus, significant improvements in CRF (+ VO_{2peak} 3ml/kg/min) can be illustrated. Similar results were obtained in a previous pilot study, which also aimed to improve CRF in allo-HCT candidates[151]. The improvement in CRF is difficult to relate due to the lack of comparable interventions and time points in treatment, although it is known that exercise therapy is an effective measure to improve CRF in patients with cancer[199]. Consequently, different effects can be achieved depending on the intervention and the subsample[145]. However, this result is primarily relevant against the background of the described risk stratification from Chapter 1.6.1 (State of the Art Impairments of CRF). Here, studies show that low VO_{2peak} values are associated with higher symptom burden during the treatment process, a lower health-related QoL and also a higher probability of mortality after treatment. Crucially, a decrease in VO_{2peak} of 1ml/kg/min seems to be associated with a higher mortality rate after allo-HCT (HR 1.13)[95]. Therefore, even small improvements could help to improve the prognosis of patients. Specifically, this means that the present intervention was able to do so (Manuscript III). Thus, it seems worthwhile to pursue this approach further and to consider it in an even more differentiated way, also because physical training seems to act on different levels. So, it must also be considered that against the background of possible cardiac damage in the course of treatment, which is a frequent complication and leads to increased morbidity and premature mortality in the long term, first indications suggest that endurance training can reduce the cardiovascular damage caused[200].

Not only endurance training is induced. In the same extent improvements of the muscle strength are crucial, because the muscle mass also possesses prognostic value (Chapter 1.6.1). The results of the PRESENT-P study show that positive but no significant developments occurred in MVIC (knee flexion change of the dominant side: +11.25 Nm) and elbow-flexor strength (change of the dominant side: +2.13 Nm). Explanatory could be that the load form during the strength training was different than during the isometric measurement itself. Whereas the motor sequence during endurance training and the CRF-assessment is comparable. However, the higher adherence (individual adherence 92% for HIIT and 85% for RE) in endurance training may also have contributed to the higher effects achieved. It is conceivable that adaptation mechanisms actually led to the improvement within a short period of time. There is increasing evidence in the literature that HIIT is a highly effective training method and can even produce better physiological adaptations compared to traditional methods (matched work). Potential effects can be observed not only

in healthy individuals but also in different patient groups. Adaptations can be demonstrated for example with an increased skeletal muscle oxidative capacity, a reduced rate of glycogen utilization and a reduced lactate production or enhanced peripheral vascular structure and function[201]. After two weeks of HIIT training, effects on increased mitochondrial volume density and mitochondrial respiration are also conceivable. However, great care must be taken in interpretation because such adaptation mechanisms are very dependent on the intervened population[202] and cannot be uncritically transferred to hemato-oncological patients. Comparably well-founded studies are lacking here. Nevertheless, a recent meta-analysis and systematic review underscore the effects of HIIT on CRF and demonstrate significant effects in cancer patients. In addition, further studies, particularly RCTs, are also required in this area[154].

Why the effects on MVIC were not significant is not clear. Speculatively, higher effects are conceivable with a larger sample. Here, too, improvements are within the realm of possibility. Although effects are only evident after 8 to 12 weeks, an increase in muscle strength has also been measured after 2-4 weeks. Neuromuscular improvements, such as muscle activation due to motor unit synchronization, muscle recruitment or increased neural activation could be the primary cause[154]. For example, strength training significantly improved hand grip strength (+2 kg). This parameter is important due to its relevance as a possible predictor for NRM (HR 2.56)[203].

Likewise, the performance in the 6MWT was significantly increased. The improvement is in the range of 30.5m and thus clinically relevant[204]. Placed in the context of allo-HCT, this means that better baseline fitness was associated with a lower total mortality rate, so improving performance on the 6MWT could be of great clinical importance. [114].

RECRUITMENT AND FEASIBILITY

Essential effects of the intervention program of the PRESENT-P study can be demonstrated. The intervention seems to be effective and well accepted in terms of exercise modalities. However, feasibility and acceptability have only been demonstrated using a small sample. It remains first of all unclear how to better structure an exercise intervention in the short period before allo-HCT. At the center of the limitation is the recruitment problem[152]. In our case, too, this has led to the discontinuation of the study and is also limited elsewhere. There are too few studies that follow purely pretraining interventions to be able to give generalizable conclusions at this level (Chapter 1.6.3). Of course, our conclusions to date are also limited by the small sample size of the PRESENT-P study. Nevertheless, successful

recruitment is certainly a prerequisite for exercise interventions to be well implemented in clinical practice. Thus, recruitment pathways need to be considered in more detail.

One of the main reasons of low recruitment is that many uncertainties exist prior to transplantation, making a concrete estimate of the timeframe difficult. It often remains unclear whether the patient will actually undergo an allo-HCT and at what point in time exactly[152]. This could differ, for example, from surgical settings in which better efficiencies have also been demonstrated[149, 205, 206].

In terms of practical implementation, this means that closer cooperation is needed between the different units involved in preparing patients for allo-HCT in advance. Specifically, cooperation between the individual specialist disciplines such as doctors, scientists and other care structures must be improved in order to start the interventional "pretraining" as early as possible.

The prerequisite for this is that adequate findings continue to describe the status of patients and that the possibilities of physical training (e.g. effects of pretraining – Manuscript III) in this context remain the subject of research. In addition, simplified access to physical exercise (e.g. in the hematology center) could become an integral part of care in the course of preparation for allo-HCT.

In summary, although physical adaptation mechanisms in muscle strength and CRF have been described including through brief training interventions, they are not clearly transferable to cancer patients or even allo-HCT-candidates. Although the effects on CRF and muscle strength exist as described[142-144], you might have to depend on the collective you are studying. Nevertheless, existing studies looking at pretraining focus on the issue of feasibility rather than recruitment, which has emerged as a critical challenge. This indicates a research gap which should be investigated in the future.

CONCLUSIONS FOR EXERCISE INTERVENTION PROFILES

Based on the findings regarding the reduced physical performance (CRF and muscle strength) prior to allo-HCT and the implementation of an exercise intervention (PRESENT-P), consequences for a possible exercise profile of the transplant candidates can be drawn. Thus, moderate training effects on the two identified limitations of our sample (reduced CRF and mainly lower extremity muscle weakness) have been well demonstrated (cardiorespiratory fitness; ES = 0.53, 95% CI = 0.13–0.94, lower extremity muscle strength; ES = 0.56, 95% CI = 0.18–0.94) [207]. Further consequences have to be considered.

A number of different influencing factors exist that induce physiological impairments (e.g. toxicity of prior therapies; influencing factors of Manuscript I and II) and can change the profile for an exercise intervention. These may also be dependent on the hematological diagnosis. For example, with regard to the population of the PRESENT-P study, it would be expected that relatively few pretreatments were given to MDS patients (31%). Thus, the treatment regimen differs in various hematologic diseases and may be less intensive in MDS (e.g. low risk, watch and wait strategy). On the other hand, different diagnoses require a variety of treatment protocols.

It may be central to identify tailored approaches to optimize the efficacy, tolerability, and safety of exercise. Current approaches based on heterogeneous collectives and the "one size fits all" approach is already being increasingly superseded[208], as current exercise recommendations indicate[2]. Future descriptions will attempt to specify a particular phenotype, taking into account the FITT-criteria. Possible responders and non-responders must be considered[208]. Through the present work, it was possible to address this recommendation and identify possible limitations and subgroups or more targeted approaches (e.g., improvement of muscle strength of the lower extremity).

The findings from Manuscript I and II help to identify patients more accurately, the PRESENT-P results (Manuskript III) illustrate highly promising signs of the feasibility and effectiveness of pretraining in the allo-HCT setting on the one hand, but also reveal limitations in the exercise implementation on the other.

6.3 Future directions

Due to the various underlying diseases, the different pretreatments, and the individual health status of allo-HCT candidates, it remains difficult to perform tailored risk stratification, although vulnerable patient groups have been identified. In the future, the subsequent exercise therapies should be possible on a patient-specific basis. However, this requires further research, including the appropriate assessments, study designs and further interprofessional effort.

IDENTIFY SUBGROUPS

Thus, an important challenge for the future will be to better identify target subgroups for exercise interventions. It is obvious that this depends, among other things, on the pre-transplant period. In this context, the suffering and treatment spectrum to which the candidates are exposed prior to allo-HCT must be taken into regard. There is potential for

optimization in future studies in the systematic recording of therapies, for example of corticosteroids (muscle wasting, weakness) or of anthracyclines (cardiotoxic type), that dose-dependent statements can also be better determined (dose-response). A concomitant decrease in hemoglobin as well as cardiac output is shown to decrease with cardiotoxic treatment, which would limit the reserve capacity for global blood flow during physical activities requiring large muscle mass, such as running or cycling[209, 210]. Therefore, further restriction to activities of daily living is conceivable.

THE DEPENDENCY OF PHYSICAL CONDITION AND PHYSICAL ACTIVITY

More attention should also be paid to physical activity in everyday life. Thus, a higher everyday activity presupposes a good physical performance and, at the same time, it is conceivable to increase the physical performance through more activity. For example, stair climbing has the potential to improve CRF under certain conditions[211].

The long pretreatment periods of the patients lead us to assume that the skeletal muscles have already been subjected to reduced utilization as a result of "multiple-caused" immobilization, which is reflected not least in the limited values of muscle strength and CRF. On the other hand, this is an important requirement for the successful performance of a higher level of physical activity. A systematic (categorization of different activity classes) and objective observation (accelerometry) would certainly be valuable to understand this dependency relationship. At the core of further investigations should remain that physical activity and the performance parameters of CRF and muscle strength can be considered modifiable. Exercise interventions and physical activity as nonpharmacological treatment for muscle wasting condition are possibly of considerable value in this regard[212]. Certainly this is a big challenge, molecular and cellular mechanisms (e.g. inflammation, mitochondrial dysfunction, dysregulation of satellite cells, protein synthesis) and multifactorial influence (e.g. lifestyle, comorbidities, hemoglobin-level and various treatments) has to be taken into account.

PATIENT'S PROFILE, TRAINING MODALITIES AND THEIR ASSESSMENTS

Further investigations should therefore systematically consider the patients individual profile, including the comorbidity burden of the patients. Against the background of the increasing age of potential allo-HCT candidates, this is becoming increasingly relevant. Not only the direct physical performance could be negatively affected, but possibly also the specific exercise intervention. At least in further studies this factor should be well documented and considered in the collective description. It is not very likely that severe

comorbidities are present, as patients need to be fit enough for allo-HCT, however, they might be ceiling more intense exercise sessions (e.g. HIIT). This should also be considered from the perspective of patients, who may face challenging allo-HCT treatment with physical training and may develop anxiety. Initial approaches are already trying to qualitatively investigate this to understand compliance and access to exercise from the patients' perspective[213, 214]. This point should probably not be underestimated. It is not only the structural and organizational barriers that prevent the early implementation of pretraining interventions, but also highly individual factors. A study of this highlights the importance of a flexible approach to physical activity, taking into account individual symptoms and preferences[215] and thus illustrates what can be considered in future research. Clearly, multifactorial barriers to accessing exercise interventions exist prior to allo-HCT, which also represents future challenges.

From the patient's point of view, the discussion should not miss the fact that the treatment of the disease is constantly changing and should therefore also be reflected in the physical exercise recommendations.

A good example of this is the growing awareness of the influence of physical exercise on the immune function and tumor microenvironment. At the same time, physical exercise in immunotherapies, which are increasingly being used, will also raise new research questions [216].

For a comprehensive statement, it is further necessary to focus on specific training modalities, but also to consider the corresponding diagnostics. For instance, different exercise therapies are capable of inducing different physiological response mechanisms[217]. In order for these to be targeted, appropriate assessments must be able to successfully identify the limitations and weaknesses in the first place.

It seems to be necessary that exercise interventions are monitored and individually adapted. In addition to the analysis of favorable conditions and suitable patients, specific exercise modalities (FITT-criteria) must also be included in the discussion. For example, the promised higher exercise intensities require the exercise therapist to be more attentive to patients and thus a closer supervision. It must be ensured that gold standard assessments (e.g. CPET) verify the patient's health status and the effectiveness of training interventions. This is certainly warranted not only in light of further scientific evidence, but also because CRF, for example, is so strongly related to survival in various patient groups that it is routinely measured as a new "vital sign"[152, 218].

Further studies should investigate whether those patients with low CRF values also have lower muscle strength. The assumption suggests itself, since there are intersections in our description (Manuscrip I and II) of the vulnerable subgroup (eg. younger or male patients have higher deviations from healthy reference values in both CRF and muscle strength). But, those aspects are not fully clarified. Improved muscle strength appears to have an effect on peak work performance in a CPET, but not on the VO_{2peak} in patients with pancreatic cancer, which could be due to changes in the underlying musculature. [191]. Such relationships need to be further explored in order to find appropriate assessment tools. Recommendations on the various survey methods already exist[219]. But care should be taken at the same time to ensure that, for rational reasons, practice-oriented care and assessment of patients does not require the performance of multiple complex and costly assessments. A CPET might have physiologically global superiority compared to other assessment procedures.

Each of the assessments used provides crucial information on patient status prior to allo-HCT and strengthens the foundation for more specific exercise recommendations and modalities. At the same time, the insights gained lead to new approaches for research questions.

In this context, it was also notable that the dynamic muscle strength (=MIPT) is subject to a higher limitation than the isometric force values (Manuscript II). The underlying mechanisms cannot be fully clarified. Speculatively, dynamic muscle strength is a more complex motion and could be more negatively influenced by previous treatment or inactivity (e.g. neuromuscular mechanisms, inter- and intramuscular coordination,). This cannot be easily clarified and requires more in-depth diagnostics (e.g. parallel EMG assessment). Certainly an important aspect, as dynamic muscle strength is essential in everyday tasks and should be considered in the planning of exercise modalities, for instance with functional training aspects.

6.4 Conclusion

Despite many adversities in planning exercise interventions before allo-HCT, there is a common and well-reasoned goal: to strengthen physical resources and capacities in allo-HCT candidates. Several approaches have already revealed promising results, and we have been able to reinforce the basis of existing outcomes.

Of course, it should not be forgotten at this point that various exercise interventions during or after allo-HCT already produce promising health effects and patients can thus be treated effectively and safely. Nevertheless, with good justification, the time *before treatment initiation* is very valuable and should be used to best prepare patients for intensive

treatment. In sum, the studies to date fall short in number and quality of sufficient evidence, as this is just the beginning of an emergent process. The future scientific work needs large RCTs with high quality assessment procedures to detect specific limitations. We were able to provide a stronger basis for the "high quality approach" with our findings. Based on these assessments, targeted exercise interventions could be induced. In this context the systematic recording of the patients' history seems to be relevant. As in the quotation at the beginning of this thesis, the guiding principle of this work is "Recognition must precede application" - „Dem Anwenden muss das Erkennen vorausgehen."

In the era of precision medicine, patient specific weaknesses should be dedicated to initiate a possible counter strategy by exercise training. The data obtained show a very encouraging approach and the present work contributed to further closing existing research gaps. It was able to better characterize a vulnerable group of hemato-oncological patients, to profile subgroups and at the same time has shown that these patients can benefit from exercise training prior to treatment initiation with allo-HCT. This may improve the chances of a successful, individually tailored treatment strategy for hematological patients.

List of abbreviations

1RM test	One repetition maximum Test
6MWD	Six-Minute-Walk Distance
ADS	Allgemeine Depressionsskala
AL	Acute leukemia
ALL	Acute lymphoblastic leukemia
allo-HCT	Allogeneic hematopoietic stem cell transplantation
AML	Acute myeloid leukemia
ATS/ACCP	American Thoracic Society/ American College of Chest Physicians
AUC	Area under the curve
BIA	Body Impedance Analyze
BMI	Body Mass Index
CCI	Charlson Comorbidity Index
CGA	Comprehensive Geriatric Assessment
cGvHD	Chronic graft-versus-host disease
CLL	Chronic lymphocytic leukemia
CML	Chronic myeloid leukemia
CPET	Cardiopulmonary exercise test
CRF	Cardiorespiratory fitness (VO_{2peak})
DLCO	Diffusion Capacity of the Lungs for Carbon Monoxide

DRI	Disease Risk Index
EBMT	European Society for Blood and Marrow Transplantation
ECOG	Eastern Cooperative Oncology Group
EMG	Electromyography
EORTC-QOL-C30	European Organisation for Research and Treatment of Cancer – Quality of Life
EPO	Erythropoietin
FEV1	Forced Expiratory Volume in 1 second
FITT	Frequency, Intensity, Time, Type
GvHD	Graft-versus-Host Disease
GVL	Graft-versus-Leukemia
Hb	Hemoglobin
HCT-CI	Hematopoietic Cell Transplantation-Comorbidity Index
HIIT	High Intensity Interval Training
HL	Hodgkin lymphoma
KKG	Fragebogen zur Erfassung der Kontrollüberzeugung zu Krankheit und Gesundheit
KPS	Karnofsky Performance Status
LVEF	Left Ventricular Ejection Fraction
MDS	Myelodysplastic Syndrome
MFI	Multidimensional Fatigue Inventory
MIPT	Maximal isokinetic peak torque
MM	Multiple myeloma
MVIC	Maximal voluntary isometric contraction

NCCN	National Comprehensive Cancer Network
NCT	National Centre for Tumor Diseases
NHL	Non-Hodgkin lymphoma
Nm	Newton meter
NRM	Non-relapse mortality
OMF	Osteomyelofibrosis
OS	Overall Survival
PAM	Predict all-cause Mortality Score
PETRA study	Physical Exercise Training versus Relaxation in Allogeneic stem cell transplantation
PMR	Progressive Muscle Relaxation
PPO	Peak Power Output
PRESENT-P study	Pre-Exercise for allogeneic stem cell transplant patients: a pilot study
PROs	Patient-reported outcomes
QoL	Quality of life
RCT	Randomized Controlled Trial
RIC	Reduced-intensity conditioning
RER	Respiratory exchange ratio
ROS	Reactive oxygen species
Rpm	Repetitions per minute
RT	Resistance Training
SAA	Severe aplastic anemia
TRM	Transplant-related mortality
UPS	Ubiquitin-proteasome system

VT	Ventilatory threshold
W	Watt
WHO	World Health Organization

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