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Effects of a home-based exercise program on physical capacity and fatigue in patients with low to intermediate risk myelodysplastic syndrome—a pilot study

Markus K Schuler[a,b,c], Leopold Hentschel[b,**], Julia Göbel[a], Ekaterina Balaian[a], Beate Hornemann[b], Julia Hoffmann[d], Michael Kramer[a], Philip Kasten[e,f], Martin Bornhäuser[a], Gerhard Ehninger[a,b], Uwe Platzbecker[a,*]

[a] Department of Internal Medicine I, University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany
[b] University Cancer Center, University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany
[c] Clinic for Internal Medicine II, HELIOS Hospital Emil von Behring, Walterhöferstraße 11, 14165 Berlin, Germany
[d] University Physiotherapy Center, University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany
[e] Department of Sports Medicine, University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany
[f] Practice for Orthopedics and Orthopedic Surgery, Tübingen, Germany

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ABSTRACT

Introduction: Fatigue is a frequent and disabling symptom in myelodysplastic syndromes (MDS). There is evidence for the benefit of exercise on fatigue in haematological malignancies, but clinical trials targeting patients with MDS do not exist.
Methods: A prospective, non-randomized feasibility trial was conducted to assess the safety and efficacy of a home-based exercise intervention in patients with MDS. Exercise schedule contained endurance or strength training in daily turns over 12 weeks. Outcome measures included 6-min walking distance (6-MWD), an ergometer check, strength measurement of lower limb, abdomen and back, quality of life and fatigue.
Results: Twenty-one patients (13 male, 8 female) were included. Median age was 66 years (range 29–87). Fifteen patients (71%) continued the program till week 12 (T1), of whom eleven patients met criteria for program completion. There were no adverse events reported due to the intervention. 6-MWD significantly improved from 580 m at T0 to 645 m at T1 ($p < 0.05$). Fatigue scores did not significantly change over time (MFI: 12.8 vs. 12.3 vs. 11.9; QLQ-C30 fatigue scale: 48.2 vs. 46.7 vs. 47.4).
Conclusion: These data provide evidence that an unsupervised outpatient exercise program is feasible and can improve physical capacity. Randomized, controlled studies implementing these interventions are warranted.

1. Introduction

Fatigue is a disabling symptom in many haematological malignancies and associated with a significant impairment in quality of life (QoL). Patients suffer from tiredness, weakness and limited capability. Fatigue involves physical, psychological, mental and social aspects, and often leads to inactivity and/or a depressive mood. The myelodysplastic syndromes (MDS) are clonal disorders of hematopoietic stem cells that are characterized by ineffective hematopoiesis that results in cytopenias, mainly anemia, and a substantial risk of progression to acute myeloid leukemia (AML). The International Prognostic Scoring System (IPSS) distinguishes four patient subgroups. While the prognosis of low and intermediate-1 risk patients (further called "lower risk MDS") is rather good, Intermediate-2 and high-IPSS risk patients (i.e. "higher risk MDS patients") have a rather dismal prognosis, even in the presence of disease-modifying therapies [1].

Anemia remains the most common objective manifestation of MDS over time [2], the extent of fatigue being associated with hemoglobin (Hb) levels [3].

* Corresponding author at: Department of Internal Medicine I, University Hospital Carl Gustav Carus, Fetscherstraße 74, 01307, Dresden, Germany.
** Corresponding author at: University Cancer Center, University Hospital Carl Gustav Carus, Fetscherstraße 74, 01307, Dresden, Germany.
E-mail addresses: Leopold.Hentschel@uniklinikum-dresden.de (L. Hentschel), Uwe.Platzbecker@uniklinikum-dresden.de (U. Platzbecker).

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Among others, fatigue is also the most prevalent and disabling patient reported outcome (PRO) as reported by more than 90% of patients [4]. Other symptoms like dyspnea, insomnia and pain affect more than half of the patients. Even more interestingly, it has been demonstrated that the level of fatigue is of prognostic value for overall survival [5].

There is increasing evidence indicating that exercise can alleviate cancer-related symptoms including fatigue in patients undergoing active treatment [6]. Most data about reduction of cancer-related fatigue due to physical exercise is derived from patients with breast cancer and prostate cancer [7]. Furthermore, the beneficial effect of physical exercise in patients with hematologic diseases, mainly in those undergoing allogeneic stem cell transplantation [8–10], has been also described. Positive effects have mainly been observed in trials with supervised exercise programs with patients undergoing active treatment [11,12]. Physical capacity has been shown to be a prognostic marker in MDS [13], but little is known about the effect of physical exercise in patients with MDS.

Therfore, we designed a feasibility study to investigate the effects of a home-based physical exercise program in patients with IPSS low to intermediate-2 risk MDS. The primary endpoint was the feasibility of an unsupervised outpatient exercise program. Among others, exploratory endpoints were changes in physical capacity and quality of life in order to get an effect size to properly design a future randomized controlled trial.

2. Material and methods

2.1. Participants

The study was approved by the local ethics committee (EK 3971120) and was designed for patients with IPSS low and intermediate-2 risk MDS. Other criteria for participation were the ability to walk and written informed consent. The main exclusion criteria included severe obesity, acute infection, severe heart failure or chronic obstructive pulmonary disease and severe neurologic disorders.

Between November 2012 and March 2014, 21 patients in our hematologic outpatient clinic were enrolled into the study. The exercise program was designed based on the current evidence and the expertise of the local physical therapist and the department of sports medicine of the University Hospital Dresden. Patients were initially screened for contraindications.

2.2. Exercise program

The exercise program was administered in unsupervised home-based sessions. At the beginning, the work-out program was explained to the patients by a physical therapist and individually adapted during one to two training sessions. The program consisted of alternating endurance and resistance workouts on 6 out of 7 days a week from entering the study (T0) until week 12 (T1). Sundays were generally “training holidays”, but could be used to compensate missed sessions during the week. Follow-up (T2) was scheduled 12 weeks after T1. Patients were encouraged to continue with exercises beyond T1. In general, exercise sessions were unsupervised, but patients were allowed to ask for additional training days with the physical therapist throughout the study period. Additionally, patients were asked to keep an exercise log.

The duration of the aerobic endurance training was scheduled between 15 and 30 min without interruption. The planned exercise intensity could be adapted to the individual’s physical condition. Before the beginning of the program, patients performed an endurance test on a bicycle ergometer with an increase of 25 W every 2 min until one of the following happened first: patients reached a level of exhaustion, patients had a lactate concentration above 3.5 mmol/l, had cardiac complaints, tachycardia (more than 180 beats per minute), or hypertension (systolic blood pressure exceeding 180 and diastolic blood exceeding 100 millimeter mercury column). ECG, heart rate and blood pressure were continuously recorded during testing. The individual workload for endurance training was set to a level of 75% of the heart rate achieved at the anaerobic threshold [14]. The physical therapist trained the patients to adapt their individual exercise based on 12–14 points resembling “slightly strenuous” and “strenuous” on the Borg scale [15,16].

Strength exercises were derived to stabilize the patients’ main muscle groups, especially those involved in sitting upright and walking. The strength exercises were thus designed to allow patients to strengthen their muscle groups to maintain performing daily activities such as walking, in order to ultimately maintain their independence. In particular, the strength program consisted of a series of exercises using the own body weight and elastic bands with one to three sets of up to 20 repetitions. Coordination exercises were performed to improve walking and balance.

2.3. Outcomes

The primary outcome was the feasibility of the combined endurance and strength exercise program in this specific patient cohort. Feasibility was considered to be achieved if more than 50% of the patients would complete the program. Completion of the program was defined if the patients finished more than 75% of the scheduled exercise days.

Secondary endpoints evaluated for explorative purpose were patients’ strength and endurance. Maximal isometric voluntary strength was used to evaluate lower body strength potential. The maximal strength of extensor muscles was measured while the patient was sitting down and extended his or her knee bent against an external resistor. Isokinetic testing was performed by using the ISOMED 2000. Trunk strength was assessed by ten repeats of alternating between 20° extension to 30° flexion with the maximum strength in a sitting position. The patient was fixed so that the axis of rotation was at the level of the iliac crest.

Endurance was measured by a 6-min walking test (6-MWD) [17] and maximum workload on bicycle ergometer. The stress-test on bicycle ergometer has been widely used in the assessment of maximal physical performance in cancer patients [16,18] and correlates well with maximal oxygen uptake [19], which is the recommended method for testing cardiorespiratory fitness [20]. The 6-MWD was introduced into the study, since it is easy to use and has been used in several clinical trials [10,21].

Further secondary endpoints included quality of life, fatigue and distress. The German version of the EORTC QLQ-C30 [22] is a standardized and validated measure of QoL. It consists of 30 questions that patients answer on a 4-step Likert-scale (ranging from “1–not at all” to “4–very much”), resulting in 5 functional scales, 9 symptom scales and a global health status/QoL scored from 0 to 100. Higher scores in functional scales and the global health status represent a better clinical status, while higher scores in symptom scales represent a higher level of symptomatology [23].

The Multidimensional Fatigue Inventory (MFI; [24]) is a well-established instrument to assess fatigue. It consists of 20 items covering five dimensions of fatigue: *general fatigue, physical fatigue, mental fatigue, reduced activity* and *reduced motivation*. Results range from 4 to 20 points per scale. Patients answer items on a five-point Likert-scale, higher scores indicate higher burden of the respective dimension measured.

The Hospital Anxiety and Depression Scale (HADS; [25]) is a standardized measure for assessing distress and identifying “cases”