Title

Low-intensity exercise therapy with high frequency improves physical function and mental and physical symptoms in patients with hematologic malignancies undergoing chemotherapy

A short running title:

Influence of exercise on hematologic malignancies

Takuya Fukushima[1, 2], Jiro Nakano[3*], Shun Ishii[2], Ayumi Natsuzako[2], Junya Sakamoto[3], Minoru Okita[1]

[1]Department of Locomotive Rehabilitation Science, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan

[2]Department of Rehabilitation, Nagasaki University Hospital, Nagasaki, Japan

[3]Department of Physical Therapy Science, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan

[*]Corresponding author

Jiro Nakano

Department of Physical Therapy Science,

Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan

Address: 1-7-1 Sakamoto Nagasaki, 852-8520 Japan

Telephone: +81-95-819-7919

E-mail address: nakano-j@nagasaki-u.ac.jp

ACKNOWLEDGEMENTS: The authors would like to thank the members of the Department of Rehabilitation, Nagasaki University Hospital and the Department of Locomotive Rehabilitation Science, Nagasaki University Graduate School of Biomedical Sciences for their support; this research would not have been possible without their leadership and cooperation.

Conflict of interest: The all authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding statements: This study was supported by JSPS KAKENHI grant number JP26282156.

ABSTRACT

Objective: This study aimed to investigate the effects of low-intensity exercise therapy (LIET) on the physical and mental symptoms and functions in patients with hematologic malignancies undergoing chemotherapy.

Methods: Forty-four patients hospitalized for chemotherapy performed LIET. The exercise intensity of LIET was defined as achieving <40% of the predicted maximum heart rate calculated using the Karvonen formula. LIET consisted of aerobic and resistance training, which was carried out on weekdays. The intervention was omitted in the case of poor general health status and strong patient refusal. Muscular and physical function, activities of daily living (ADLs), psychological distress, and quality of life (QOL) were evaluated upon initiation of rehabilitation and at discharge. Participants were divided into high- and low-frequency groups according to their LIET frequency. Two-way repeated measures analysis of variance was used for statistical analysis.

Results: In the high-frequency group, muscle function was maintained, while physical function, ADLs, psychological distress, and QOL were significantly improved. However, in the low-frequency group, muscle function of the lower limb was significantly reduced and no other improvement was observed.

Conclusion: LIET could be a potential treatment strategy for patients with hematologic malignancies undergoing chemotherapy who are unable to perform mid- or high-intensity exercise.

Keywords: hematologic malignancy, chemotherapy, low-intensity exercise therapy, rehabilitation, muscle function, physical function.

INTRODUCTION

About 918,000 and 45,000 patients are annually diagnosed with hematologic malignancies, such as lymphoma, leukemia, and multiple myeloma, in the world and Japan, respectively (Felay et al., 2015; Hori et al., 2015). Chemotherapeutic treatment for hematologic malignancies can induce physical and mental symptoms such as pancytopenia, derived from nutritional deficiencies and bone marrow suppression (Knight et al., 2004; Lyman et al., 2016; Kantarjian et al., 2007; Dehghani et al., 2015), nausea, vomiting, anorexia (Dehghani et al., 2015; Grunberg et al., 2010), cancer-related fatigue (CRF) (Hjermstand et al., 2005), anxiety and depression (Hall et al., 2016; Bergerot al., 2015), as well as symptoms of hematologic malignancy itself. These symptoms result in decreased physical activity (Elter et al., 2009), leading to physical function deterioration possibly manifesting as decreased muscle strength, including handgrip and quadriceps strength (Vermaete et al., 2011). Furthermore, these symptoms and physical function degradation have negative impacts on patients' quality of life (QOL) (Oerlemans et al., 2011). The management of symptoms and declining physical function is crucial in patients with hematologic malignancy undergoing chemotherapy.

With regard to the rehabilitation of patients with malignancies, aerobic and resistance exercises are usually adopted (Rock et al., 2012; Schmitz et al., 2010). There exist several clinical studies on the effects of exercise in patients with hematologic malignancy. Courneya et al. (Courneya et al., 2009) showed that a 12-week aerobic exercise regimen using an ergometer significantly improved cardiovascular fitness, lean body mass, CRF, and depression in patients with lymphoma. Similarly, Furzer et al. (Furzer et al., 2016) demonstrated the effects of aerobic and resistance exercise on cardiovascular fitness, muscle strength, and CRF in patients with hematologic malignancies. Furthermore, Alibhai et al. (Alibhai et al., 2015) revealed that aerobic, resistance, and flexibility exercises had positive effects on aerobic fitness, muscle strength, and CRF in patients with acute myeloid leukemia. It is therefore considered that exercise is useful for improving physical function and symptomatology in patients with hematologic malignancies. However, mid- or high-level intensity exercise is often difficult to apply in the inpatient population due to the aforementioned effects related to chemotherapy. For this reason, low-intensity exercise therapy (LIET) set at 40% or less of the predicted maximum heart rate calculated by the Karvonen formula (Karvonen et al., 1957) is performed in clinical settings.

Morishita et al. (Morishita et al., 2013) reported on patients who underwent allogeneic hematopoietic stem cell transplantation that were grouped according to physical therapy frequency. The high-frequency group showed a significantly lesser decline than the low-frequency group with respect to physical functioning and QOL. We hypothesized that physical function, including physical and mental symptoms, could be improved when LIET was performed at a high frequency, despite the low exercise intensity. To the best of our knowledge, no reports have determined the effects of LIET on patients with hematologic malignancies to date; therefore, we investigated the effects of LIET on physical function and the mental and physical symptoms in patients with hematologic malignancies undergoing chemotherapy.

METHODS

Study design and participants

This was a longitudinal, observational study conducted at Nagasaki University Hospital. This study was approved by the hospital ethics committee (approval number: 15072757), and written informed consent was obtained from all participants prior to study enrollment. The inclusion criteria were as follows: (1) inpatients diagnosed with a hematologic malignancy, (2) hospitalization for chemotherapeutic treatment, (3) prescription for rehabilitation, (4) age >20 years, (5) patients who understood the evaluation content of muscle and physical function, and activities of daily living (ADLs) and did not show rejection, and (6) those who could fill questionnaires by themselves. The exclusion criteria were as follows: (1) communication difficulties, (2) poor general health status, (3) severe heart disease, (4) severe respiratory disease, (5) hepatic or renal failure, and (6) cerebrovascular or orthopedic diseases that could influence muscle and physical function.

The sample size was calculated using a sample size calculation software (G*Power version 3.1.9.2 for Windows; http://www.gpower.hhu.de) and was determined based on the change in muscle thickness (Galvão et al., 2006). With the effect size calculated from the mean and standard deviation, the statistical power and level of significance for the study were set at 0.8 and 0.05, respectively, and the sample size for each group was calculated as 14. However, the effect size in this study appeared to be smaller than in the previous study (Galvão et al., 2006), because the intervention period was shorter. Therefore, we sought to recruit 20 patients in order to achieve adequate statistical power.

Intervention

All participants performed LIET from the initiation of rehabilitation until their discharge on weekdays. Based on the report of Furzer et al. (Furzer et al., 2016), we adopted a mixed exercise program consisting of resistance training and aerobic exercise. LIET was set at 20 to 40 minutes, once a day, for up to 5 times per week. This program promoted as much walking as possible, up and down the stairs, in 1 to 2 sets. Resistance training comprised of the following: one set of 10 to 20 flexion and extension exercises of the hip, knee, and elbow joints followed by the addition of 0 to 2 kg weight loads for 1 to 2 sets, 5 to 20 times standing up or calf raises for 1 to 2 sets, and 5 squats as one set. The ergometer was set at low load for 5 to 10 minutes, which comprised the aerobic exercise. These programs were carried out one set per day. Davis et al. (Davis et al., 1975) reported that the Karvonen formula was a reasonably accurate method for estimating exercise intensity and that a low-intensity exercise was defined as an exercise with 40% or less heart rate reserve. The exercise intensity was set at 40% or less of the predicted maximum heart rate calculated by the Karvonen formula and set to “somewhat hard” rated as “4” on the modified Borg scale (Borg, 1982). As a general rule, LIET was performed on weekdays. In the low-frequency group, it did not intentionally reduce the intervention frequency. In the case of high blood pressure (shrinkage period blood pressure ≧200 mmHg or diastolic blood pressure ≧120 mmHg), chest pain, atrial fibrillation, ventricular tachycardia, dyspnea, high fever, dizziness, and strong patient refusal, we consulted with the doctor and the intervention was omitted on that day. We defined intervention frequency as the value of the number of intervention days divided by the number of weekdays from the initiation of rehabilitation until discharge.

Measurements

We evaluated the participants' muscle and physical functions, ADLs, psychological distress, and QOL at the start of rehabilitation (baseline) and at discharge (post-treatment). Baseline age, sex, body mass index (BMI), cancer type, blood biochemical parameters (hemoglobin, C-reactive protein, albumin, total protein, lymphocytes), days since hospitalization, days since chemotherapy, and disease duration data were collected from the medical records. The length of hospital stay was recorded upon discharge.

Muscle function

Handgrip strength and isometric knee extensor strength were assessed as markers of muscle strength. Handgrip strength was measured using a standard adjustable-handle dynamometer (TKK 5101; Takei Scientific Instruments Co. Ltd., Niigata, Japan). The measurements were taken in the standing position, with their arm held in zero abduction and flush against the body. A single attempt of maximum value was recorded in kilogram force (kgf). Isometric knee extensor strength was measured using hand-held dynamometers (HHDs; μ-tas F-1; ANIMA Co., Tokyo, Japan) in the sitting position, on a chair with the knee joint flexed at approximately 90°. The HHD sensor was placed on the distal anterior surface of the lower leg, and a belt was placed over the HHD and tied to the leg of the chair. Knee joint extension at maximum exertion was performed for approximately 5 s, and was repeated twice. The result was expressed in kgf, and the highest value was entered into the analysis.

According to a previous study (Tillquist et al., 2014), muscle mass was quantified by measuring the thickness of the vastus intermedius plus rectus femoris muscles. Muscle thickness was measured using an ultrasound device (SeeMore^{TM}, Interson Corp., CA, USA) in the supine position, with the legs lying flat and relaxed in extension. A straight line was drawn between the anterior superior iliac spine and the upper margin of the patella, and then, it was measured at 10 cm proximal to the patella on this line. The result was recorded in millimeters (mm).

Physical function

Physical function was evaluated using a 10-meter walk test (10MWT) and a timed up and go test (TUGT). They are relatively easy to conduct among inpatients, as these tests are simple and do not require special equipment. The result of 10MWT was a marker of gait velocity, with the participants walking unassisted at a maximum speed (Bohannon, 1997). TUGT was measured as an index of functional mobility, which consisted of walking speed, strength, and balance. Participants were instructed to rise from a chair of standardized height, walk a fixed distance of 3 meters, turn, return to the chair, and sit down again (Podsiadlo et al., 1991). Previous studies reported that TUGT and 10MWT strongly correlated with 6MWT, which is an index of exercise capacity (Dalgas et al., 2012; Ng et al., 2005). The reliability of 10MWT (Bohannon, 1997) and the validity and reliability of TUGT have been previously reported (Podsiadlo et al., 1991; Brooks et al., 2006). The duration for a single attempt of a 10-meter walk was recorded in seconds (sec), and after several TUGT attempts were performed, the fastest time was recorded also in seconds.

Activities of daily living (ADLs)

ADLs were evaluated using the Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) and the Functional Independence Measure (FIM). The ECOG PS scoring was defined as follows: 0, fully active; 1, restricted in physically strenuous activity but ambulatory and able to perform work of a light or sedentary nature; 2, ambulatory and capable of all self-care but unable to perform any work activities, up and about more than 50% of waking hours; 3, capable of only limited self-care, confined to a bed more than 50% of waking hours; 4, completely disabled, totally confined to a bed (Oken et al., 1982). FIM assessed function and the need for assistance. It consists of an 18-item scale that measures independence in performing tasks of feeding, grooming, dressing, toileting, mobility, and cognition (Kidd et al., 1995). Each item is rated on a scale of 1–7 (1=total assistance, 5=needs supervision, 6=modified independence, 7=independent). A low score reflects the burden of care in each area measured. The reliability and validity of FIM have been previously reported (Kidd et al., 1995; Heinemann et al., 1993).

Psychological distress

The sum-total score of the Hospital Anxiety and Depression Scale (HADS) was used to evaluate psychological distress. This is a widely used and validated questionnaire to assess psychological morbidity in cancer patients (Vodermaier et al., 2011), comprising 7-item anxiety and 7-item depression subscales. Items are rated 0 (best status) to 3 (worst status), and the scores of each subscale are summed up. Possible scores for each subscale range from 0 to 21 points. Higher scores reflect worse psychological distress.

Quality of Life (QOL)

QOL was measured using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-C30 (QLQ-C30). The EORTC QLQ-C30 is a cancer-specific self-report questionnaire consisting of the global QOL scale (2 items), 5 functional scales (physical, role, emotional, cognitive, and social functioning), 3 symptom scales (fatigue, pain and nausea/vomiting), and 6 single items. The two items of the global QOL scale apply a modified 7-point linear analogue scale. All other items are scored on a 4-point categorical scale ranging from 1 (not at all) to 4 (very much). All scales and single items are converted to a 0–100 scale. For the global QOL scale and five functional scales, a higher score represents a better level of functioning. On the other hand, for the symptom scales and items, a high score means a higher level of symptoms (Aaronson et al., 1993).

Statistical analysis

Participants were divided into two groups based on the LIET intervention frequency. LIET was generally performed on weekdays. The intervention was omitted in the case of poor general health status and strong patient refusal. Accordingly, some patients performed LIET at a high intervention frequency (about 5 times per week), whereas some patients performed LIET at a lower intervention frequency. Upon hospital discharge, the median intervention frequency was calculated retrospectively and was used as the criteria for the division of patients into two groups according to the previous study (Morishita et al., 2013). The two groups consisted of a high-frequency (HF; intervention frequency greater than the median) and a low-frequency (LF; intervention frequency less than the median) group.

Statistical analysis was performed using IBM SPSS Statistics version 23 software (IBM Corp., Armonk, NY, USA). Data were presented as mean±standard deviation (SD), and missing values were excluded from the analysis. The comparison of demographic and clinical characteristics data was performed using the Mann-Whitney U-test and the chi-square test. Two-way repeated measures analysis of variance (ANOVA) was performed to compare the effects between the two groups (HF and LF), time (baseline and post-treatment), and interaction between the group and time. Values of $P < 0.05$ were considered statistically significant.

RESULTS

The patient selection process is shown in Fig. 1. Forty-four of the 90 eligible patients with hematologic malignancies (21 men, 23 women) participated in the study. Table 1 shows the demographic and clinical characteristics data. The mean age was 68.2±10.7 and the mean BMI was 21.1±3.4 kg/m^2. Most patients (72.7%) were diagnosed with lymphoma. The days since hospitalization and chemotherapy were 8.1±9.5 and 1.7±8.7 days, respectively. The duration of hospital stay was 40.5±23.3 days, and the disease duration was 667.5±1308.3 days.

The median intervention frequency in all patients was 0.82. Patients were divided into HF and LF groups according to the median intervention frequency. The intervention frequencies of the HF and LF groups were 0.93±0.06 and 0.66±0.14, respectively. There were no significant differences in demographic or clinical characteristics data (Table 1). No significant differences were observed between the groups in terms of body weight at baseline and post-treatment. Both groups significantly decreased their total body weight from baseline to post-treatment, and there were no significant interactions between the group and time (Table 2).

Muscle function

No significant differences were observed between the two groups in terms of handgrip strength, isometric knee extensor strength, or muscle thickness at baseline and post-treatment. The HF group showed no significant changes in all parameters of muscle function from baseline to post-treatment. On the other hand, in the LF group, isometric knee extensor strength and muscle thickness decreased significantly from baseline to post-treatment. No significant interactions were observed between the group and time in all parameters of muscle function (Table 2).

Physical function

No significant differences were observed between the LF and HF groups in 10MWT and TUGT at baseline. In both 10MWT and TUGT, the HF group showed a significant improvement from baseline to post-treatment; however, there were no changes in the LF group. No significant interactions between the group and time in both 10MWT and TUGT were observed (Table 2).

ADL

Although LF showed no significant differences from baseline to post-treatment, HF significantly improved in both ECOG PS and FIM from baseline to post-treatment. Significant interactions were seen between the group and time (Table 2).

Psychological distress

Based on the HADS score, no significant differences were observed between the HF and LF groups in both anxiety and depression scores at baseline. A significant improvement in anxiety score was shown from baseline to post-treatment in both the HF and LF groups, but this interaction was not confirmed between the two groups. Depression scores did not show any significant changes in both groups (Table 3).

QOL

Although the LF group did not show any significant improvements, the HF group significantly improved in global health, physical, emotional, and cognitive function from baseline to post-treatment. Similarly, fatigue, pain, and insomnia on the symptom scale were improved only in the HF group, but not in the LF group. Significant interactions were seen between the group and time in terms of cognition and insomnia (Table 4).

DISCUSSION

This was an evaluation study that examined the effects of LIET, which was performed in clinical settings, on physical function and the mental and physical symptoms of patients with hematologic malignancies undergoing chemotherapy. Although the effect of exercise therapy of mid- to high-intensity on patients has previously been reported, to the best of our knowledge, this is the first study to examine the effect of LIET on patients with hematologic malignancies.

The influence of chemotherapy was equal for both groups, as both groups experienced similar changes in body weight. Previous studies have shown that exercise therapy of mid- to high- intensity improved both arm and handgrip strength (Furzer et al., 2016; Alibhai et al., 2015). However, the results of the present study showed that LIET did not significantly improve the handgrip strength of either group. Although LIET did not improve the handgrip strength, it is possible that handgrip strength could have been maintained irrespective of the frequency. Although both mid- to high-intensity exercise therapies have been previously shown to improve muscle strength of the lower limbs in patients with hematologic malignancies (Courneya et al., 2009; Furzer et al., 2016; Alibhai et al., 2015), LIET did not significantly improve muscle function in both our study groups. In contrast, the isometric knee extensor strength and muscle thickness were significantly reduced in the LF group. The lower limb muscles which would be affected by prevented syndrome more easily (de Bore et al., 2008). LIET could not stop the progression of disuse-related muscle atrophy in the hospital based on low frequency enforcement. In the HF group, the isometric knee extensor strength and muscle thickness could be maintained significantly. Thus, these results showed that LIET could maintain muscle function in the hospital setting when it is performed with high frequency.

As for 10MWT, LIET improved gait velocity among patients in the HF group, but not in the LF group. These results revealed that even if the exercise intensity is low, LIET with high frequency leads to an improvement in gait ability. Chang et al. (Chang et al., 2008) reported that a 3-week intervention of simple exercise, consisting of 12 minutes walking, 5 days per week, could improve the gait ability in patients with leukemia undergoing chemotherapy, supporting our findings. Wang et al. showed that increased CRF significantly compromised walking ability in patients with leukemia and lymphoma (Wang et al., 2002). Carter et al. revealed that improved ease of walking was associated with lower depressive symptomatology (Carter et al., 2018). In other words, it is assumed that the significant reduction of CRF and psychological distress in the HF group resulted in improved walking ability. Similarly, the HF group showed significant improvement in TUGT. TUGT can assess muscle strength in addition to walking ability (Podsiadlo et al., 1991); however, LIET could not increase muscle volume and strength due to the low exercise intensity in this study. It was assumed that the improvement of walking ability contributed to improved TUGT.

Similar to physical function, only the HF group showed significant improvements in ADLs, which were evaluated by ECOG PS and FIM. A previous study by van den Dungen et al. (van den Dungen et al., 2014), indicated that mid- to high-intensity exercise therapy improved the ADLs in patients with advanced malignancies. In other words, LIET might recover ADLs in patients similar to that demonstrated by mid- to high-intensity exercise when the former is performed at a higher frequency.

However, it was impossible to definitively determine whether low-frequency exercise had any effect on ADLs in the LF group because the value of FIM in both groups was very high at baseline (a perfect score of FIM is 126 and the LF group was 120.2 ± 7.2 points). There was a possibility that the effect of LIET could not be reflected well by FIM points in this study. The ECOG PS differed between the HF and LF groups, although it was only improved in the HF group. ECOG PS reflected the physical activity of inpatients. It was presumed that the recovery of ECOG PS—possibly due to the improvement of physical function in the HF group—allowed for the expansion of physical activity among inpatients with hematologic malignancy undergoing chemotherapy.

According to previous studies, psychological distress has a negative effect on muscle function and physical activity (Galliano-Castillo et al., 2014; Kilgour et al., 2010; Vardar-Yagli et al., 2015), which can also be improved by mid- to high- intensity exercise therapy for patients with hematologic malignancies (Courneya et al., 2009; Alibhai et al., 2015). It has also been reported that improvements in psychological distress are associated with exercise of low intensity, such as walking (Chen et al., 2015). Therefore, improvements in anxiety and depression after LIET at a high frequency were expected. As a result, anxiety scores of HADS were improved in both groups, albeit no difference was noted between the two groups. It was not clear whether LIET could improve anxiety regardless of intervention frequency, or whether other treatments such as pharmacotherapy affected anxiety levels in all patients. Furthermore, depression scores did not change from baseline to post-treatment in both groups. LIET in this study might affect psychological distress in patients with hematologic malignancy undergoing chemotherapy in the hospital.

Significant interactions between the HF and LF groups were observed in only the cognitive function and insomnia symptoms on the QLQ-C30. In the HF group, global health; physical, role, emotional, and cognitive functioning; and fatigue, pain, and insomnia on the symptom scale significantly improved. On the other hand, there was no improvement in the LF group. Vallance et al. (Vallance et al., 2005) showed favorable associations between regular exercise and physical functioning, decreased fatigue, and overall QOL in a cross-sectional survey of hematologic malignancy survivors. Thus, some functions and symptoms in the HF group were improved by LIET at high frequency as regular exercises, which might lead to improvements in the QOL of patients with hematologic malignancy undergoing chemotherapy.

There were some limitations to this study. First, the sample size was small and there was a deficiency of measurement items. The sample size was calculated from the change in muscle thickness pre- and post-intervention. Considering that this study was an observational and evaluation study, the sample size calculation was acceptable and the number of samples was sufficient. However, we cannot rule out the possibility that patients with the same characteristics are recruited. From the viewpoint of generalization, we believe that a multicenter investigation with a large sample size will be necessary. We experienced difficulties with the inclusion of patients and the completion of all measurements. In addition, endurance activities, such as the 6-minute walk test, and physical activities, such as the number of steps, should be evaluated to determine the physical function of patients. Second, the effect of LIET could not be clarified precisely because this study is a longitudinal, observational study. The influences of the pathologic changes of hematologic malignancy and the pharmacotherapies, including chemotherapy, cannot be completely excluded as influencing factors. It is necessary to verify the effects of LIET by performing randomized controlled trials in the future.

In this study, we investigated the effects of LIET on patients with hematologic malignancy undergoing chemotherapy by dividing the patients according to their intervention frequency. The patients who practiced LIET at a higher-frequency maintained their muscle function, and demonstrated significant improvements in their physical function, ADLs, and QOL. In contrast, muscle function of the lower limbs was significantly reduced in patients who practiced LIET at a lower-frequency, and no other improvements were observed in these patients. These results indicate that LIET is effective for improving physical functions, ADLs, and some symptoms in these patients. Therefore, we conclude that LIET could be considered as a potential treatment strategy for patients with hematologic malignancy undergoing chemotherapy who are unable to adapt to mid- or high-intensity exercise therapy.

REFERENCES

- Aaronson, N. K., Ahmedzai, S., Bergman, B., Bullinger, M., Cull, A., Duez, N. J., Filiberti, A., Flechtner, H., Fleishman, S. B., de Haes, J. C. (1993). The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international carry trials in oncology. *Journal of the National Cancer Institute*, 85, 365–376.
- Alibhai, S. M., Durbano, S., Breunis, H., Brandwein, J. M., Timilshina, N., Tomlinson, G. A., Oh, P. I., Culos-Reed, S. N. (2015). A phase II exercise randomized controlled trial for patients with acute myeloid leukemia undergoing induction chemotherapy. *Leukemia Research*, 39, 1178–1186.
- Bergerot, C. D., Clark, K. L., Nonino, A., Waliany, S., Buso, M. M., Loscaizo, M. (2015). Course of distress, anxiety, and depression in hematologic cancer patients: association between gender and grade of neoplasm. *Palliative & Supportive Care*, 13, 114–123.
- Bohannon, R. W. (1997). Comfortable and maximum walking speed of adults aged 20-79 years: reference values and determinants. *Age and Ageing*, 26, 15–19.
- Borg, G. A. (1982). Psychophysical bases of perceived exertion. *Medicine and Science in Sports and Exercise,* 14, 377–381.
- Brooks, D., Davis, A. M., Naglie, G. (2006). Validity of 3 physical performance measures in inpatient geriatric rehabilitation. *Archives of Physical Medicine and Rehabilitation*, 87, 105–110.
- Carter, S. J., Hunter, G. R., Norian, L. A., Turan, B., Rogers, L. Q. (2018). Ease of walking associates

with greater free-living physical activity and reduced depressive symptomology in breast cancer survivors: pilot randomized trial. *Supportive Care in Cancer*, 26, 1675–1683.

- Chang, P. H., Lai, Y. H., Shun, S. C., Lin, L. Y., Chen, M. L., Yang, Y., Tsai, J. C., Huang, G. S., Cheng, S. Y. (2008). Effects of a walking intervention on fatigue-related experiences of hospitalized acute myelogenous leukemia patients undergoing chemotherapy: a randomized controlled trial. *Journal of Pain and Symptom Management*, 35, 524–534.
- Chen, H. M., Tsai, C. M., Wu, Y. C., Lin, K. C., Lin, C. C. (2015). Randomised controlled trial on the effectiveness of home-based walking exercise on anxiety, depression and cancer-related symptoms in patients with lung cancer. *British Journal of Cancer*, 112, 138–445.
- Courneya, K. S., Sellar, C. M., Stevinson, C., McNeely, M. L., Peddle, C. J., Friedenreich, C. M., Tankel, K., Basi, S., Chua, N., Mazurek, A., Reiman, T. (2009). Randomized controlled trial of the effects of aerobic exercise on physical functioning and quality of life in lymphoma patients. *Journal of Clinical Oncology*, 27, 4605–4612.
- Dalgas, U., Severinsen, K., Overgaard, K. (2012). Relations between 6 minute walking distance and 10 meter walking speed in patients with multiple sclerosis and stroke. *Archives of Physical Medicine and Rehabilitation*, 93, 1167–1172.
- Davis, J. A., Convertino, V. A. (1975). A comparison of heart rate methods for predicting endurance training intensity. *Medicine and Science in Sports,* 7, 295–298.

- de Bore, M. D., Seynnes, O. R., di Prampero, P. E., Pisot, R., Mekjavić, I.B., Biolo, G., Narici, M. V. (2008). Effect of 5 weeks horizontal bed rest on human muscle thickness and architecture of weight bearing and non-weight bearing muscles. *European Journal of Applied Physiology*, 104, 401–407.
- Dehghani, M., Haddadi, S., Vojdani, R. (2015). Signs, symptoms and complications of non-Hodgkin's lymphoma according to grade and stage in South Iran. *Asian Pacific Journal of Cancer Prevention*, 16, 3551–3557.
- Elter, T., Stipanov, M., Heuser, E., von Bergwelt-Baildon, M., Bloch, W., Hallek, M., Baumann, F. (2009). Is physical exercise possible in patients with critical cytopenia undergoing intensive chemotherapy for acute leukaemia or aggressive lymphoma? *International Journal of Hematology*, 90, 199–204.
- Ferlay, J., Soerjomataram, I., Dikshit, R., Eser, S., Mathers, C., Rebelo, M., Parkin, DM., Forman, D., Bray, F. (2015). Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *International Journal of Cancer*, 136, E359–386.
- Furzer, B. J., Ackland, T. R., Wallman, K. E., Petterson, A. S., Gordon, S. M., Wright, K. E., Joske, D. J. (2016). A randomised controlled trial comparing the effects of a 12-week supervised exercise versus usual care on outcomes in haematological cancer patients. *Supportive Care in Cancer*, 24, 1697–1707.
- Galliano-Castillo, N., Ariza-Garcia, A., Cantarero-Villanueva, I., Fernandez-Lao, C., Diaz-Rodriguez,

L., Arroyo-Morales, M. (2014). Depressed mood in breast cancer survivors: associations with physical activity, cancer-related fatigue, quality of life, and fitness level. *European Journal of Oncology Nursing*, 18, 206–210.

- Galvão, D. A,, Nosaka, K., Taaffe, D. R., Spry, N., Kristjanson, L. J., McGuigan, M. R., Suzuki, K., Yamaya, K., Newton, R. U. (2006). Resistance training and reduction of treatment side effects in prostate cancer patients. *Medicine and Science in Sports and Exercise,* 38, 2045–2052.
- Grunberg, S. M., Warr, D., Gralla, R. J., Rapoport, B. L., Hesketh, P. J., Jordan, K., Espersen, B. T. (2010). Evaluation of new antiemetic agents and definition of antineoplastic agent emetogenicity--state of the art. *Supportive Care in Cancer* 19, S43–S47.
- Hall, A. E., Sanson-Fisher, R. W., Carey, M. L., Paul, C., Williamson, A., Bradstock, K., Campbell, H. S. (2016). Prevalence and associates of psychological distress in haematological cancer survivors. *Supportive Care in Cancer*, 24, 4413–4422.
- Heinemann, A. W., Linacre, J. M., Wright, B. D., Hamilton, B. B., Granger, C. (1993). Relationship between impairment and physical disability as measured by the functional independence measure. *Archives of Physical Medicine and Rehabilitation*, 74,566–573.
- Hjermstand, M. J., Fossa, S. D., Oldervoll, L., Holte, H., Jacobsen, A. B., Loge, J. H. (2005). Fatigue in long-term Hodgkin’s disease survivors: a follow-up study. *Journal of Clinical Oncology*, 23, 6587–6595.

- Hori, M., Matsuda, T., Shibata, A., Katanoda, K., Sobue, T., Nishimoto, H., Japan Cancer Surveillance Research Group. (2015). Cancer incidence and incidence rates in Japan in 2009: a study of 32 population-based cancer registries for the Monitoring of Cancer Incidence in Japan (MCIJ) project. *Japanese Journal of Clinical Oncology*, 45, 884–891.
- Kantarjian, H., Giles, F., List, A., Lyons, R., Sekeres, M. A., Pierce, S., Deuson, R., Leveque, J. (2007). The incidence and impact of thrombocytopenia in myelodysplastic syndromes. *Cancer*, 109, 1705–1714.
- Karvonen, M. J., Kentala, E., Mustala, O. (1957). The effects of training on heart rate; a longitudinal study. *Annales Medicinae Experimentalis et Biologiae Fenniae*, 35, 307–315.
- Kidd, D., Stewart, G., Baldry, J., Johnson, J., Rossiter, D., Petruckevitch, A., Thompson, A. J. (1995). The Functional Independence Measure: a comparative validity and reliability study. *Disability and Rehabilitation*, 17, 10–14.
- Kilgour, R. D., Vigano, A., Trutschnigg, B., Hornby, L., Lucar, E., Bacon, S. L., Morais, J. A. (2010). Cancer-related fatigue: the impact of skeletal muscle mass and strength in patients with advanced cancer. *Journal of Cachexia, Sarcopenia and Muscle*, 1, 177–185.
- Knight, K., Wade, S., Balducci, L. (2004). Prevalence and outcomes of anemia in cancer: a systematic review of the literature. *The American Journal of Medicine*, 116 suppl 7A, 11S–26S.
- Lyman, G. H., Poniewieraski, M. S., Culakova, E. (2016). Risk of chemotherapy-induced

neutropenic complications when treating patients with non-Hodgkin lymphoma. *Expert Opinion on Drug Safety*, 15, 483–492.

- Morishita, S., Kaida, K., Setogawa, K., Kajihara, K., Ishii, S., Ikegame, K., Kodama, N., Ogawa, H., Domen, K.. (2013). Safety and feasibility of physical therapy in cytopenic patients during allogeneic haematopoietic stem cell transplantation. *European Journal of Cancer Care*, 22, 289–299.
- Ng, S. S., Hui-Chan, C. W. (2005). The timed up & go test; its reliability and association with lower-limb impairments and locomotor capacities in people with chronic stroke. *Archives of Physical Medicine and Rehabilitation*, 86, 1641–1647.
- Oerlemans, S., Mols, F., Nijziel, M. R., Lybeert, M., van de Poll-Franse, L. V. (2011). The impact of treatment, socio-demographic and clinical characteristics on health-related quality of life among Hodgkin's and non-Hodgkin's lymphoma survivors: a systematic review. *Annals of Hematology*, 90, 993–1004.
- Oken, M. M., Creech, R. H., Tormey, D. C., Horton, J., Davis, T. E., McFadden, E. T., Carbone, P. P. (1982). Toxicity and response criteria of the Eastern Cooperative Oncology Group. *American Journal of Clinical Oncology*, 5, 649–655.
- Podsiadlo, D., Richardson, S. (1991). The timed "Up & Go": a test of basic functional mobility for frail elderly persons. *Journals of the American Geriatrics Society*, 39, 142–148.
- Rock, C. L., Doyle, C., Demark-Wahnefried, W., Meyerhardt, J., Courneya, K. S., Schwartz, A.

L., Bandera, E. V., Hamilton, K. K., Grant, B., McCullough, M., Byers, T., Gansler, T. (2012). Nutrition and physical activity guidelines for cancer survivors. *CA: A Cancer Journal for Clinicians*, 62, 243–274.

- Schmitz, K. H., Courneya, K.S., Matthews, C., Demark-Wahnefried, W., Galvão, D. A., Pinto, B. M., Irwin, M. L., Wolin, K. Y., Segal, R. J., Lucia, A., Schneider, C. M., von Gruenigen, V. E., Schwartz, A. L., American College of Sports Medicine. (2010). American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. *Medicine & Science in Sports & Exercise*, 42, 1409–1426.
- Tillquist, M., Kutsogiannis, D. J., Wischmeyer, P. E., Kummerlen, C., Leung, R., Stollery, D., Karvellas, C. J., Preiser, J. C., Bird, N., Kozar, R., Heyland, D. K. (2014). Bedside ultrasound is a practical and reliable measurement tool for assessing quadriceps muscle layer thickness. *Journals of Parenteral and Enteral Nutrition*, 38, 886–890.
- Vallance, J. K., Courneya, K. S., Jones, L. W., Reiman, T. (2005). Differences in quality of life between non-Hodgkin's lymphoma survivors meeting and not meeting public health exercise guidelines. *Psychooncology*, 14, 979–991.
- van den Dungen, I. A., Verhagen, C. A., van der Graaf, W. T., van den Berg, J. P., Vissers, K. C., Engels, Y. (2014). Feasibility and impact of a physical exercise program in patients with advanced cancer: a pilot study. *Journal of Palliative Medicine*, 17, 1091–1098.

- Vardar-Yagli, N., Sener, G., Saglam, M., Calik-Kutukcu, E., Arikan, H., Inal-Ince, D., Savci, S., Altundag, K., Kutluk, T., Ozisik, Y., Kaya, E. B. (2015). Associations among physical activity, comorbidity, functional capacity, peripheral muscle strength and depression in breast cancer survivors. *Asian Pacific Journal of Cancer Prevention*, 16, 585–589.
- Vermaete, N., Wolter, P., Verhoef, G., Gosselink, R. (2014). Physical activity and physical fitness in lymphoma patients before, during, and after chemotherapy: a prospective longitudinal study. *Annals of Hematology*, 93, 411–424.
- Vodermaier, A., Millman, R. D. (2011). Accuracy of the Hospital Anxiety and Depression Scale as a screening tool in cancer patients: a systematic review and meta-analysis. *Supportive Care in Cancer*, 19, 1899–1908.
- Wang, X. S., Giralt, S. A., Mendoza, T. R., Engstrom, M. C., Johnson, B. A., Peterson, N., Broemeling, L. D., Cleeland, C. S. (2002). Clinical factors associated with cancer-related fatigue in patients being treated for leukemia and non-Hodgkin's lymphoma. *Journal of Clinical Oncology*, 20, 1319–1328.

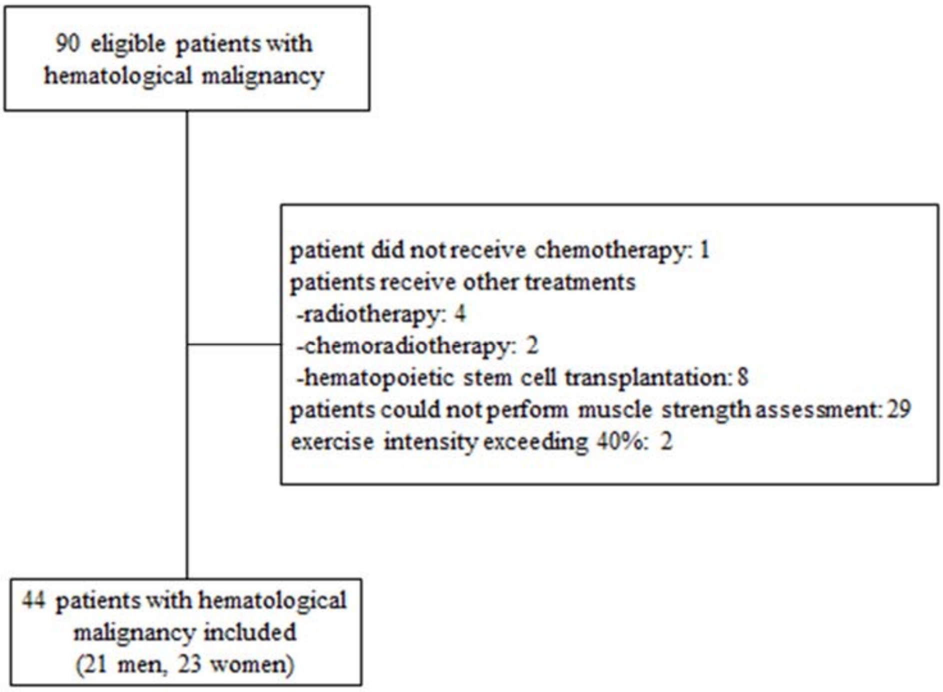

Fig.1 Flow chart of the recruitment procedure

Table 1. Demographic and clinical characteristics of participants at the start of rehabilitation (baseline)

Parameters	Total (n=44)	Total min-max	HF group (n=22)	LF group (n=22)	P-value
Age, years	68.2±10.7	41-86	68.0±8.6	68.4±12.4	0.742
Sex, n (%)					0.365
Male	21 (47.7)		12 (54.5)	9 (40.1)	
Female	23 (52.3)		10 (45.5)	13 (59.9)	
Body weight (kg)	54.4±11.7	35.3-92.2	56.3±13.7	52.5±9.3	0.292
BMI, kg/m^2	21.1±3.4	14.6-31.8	21.5±4.0	20.7±2.8	0.589
Hemoglobin (g/dL)	10.3±2.3	5.5-15.9	10.3±2.6	10.3±1.9	0.814
CRP (mg/dL)	1.1±2.1	0.02-10.6	0.6±1.1	1.6±2.7	0.635
Albumin (g/dL)	3.5±0.6	2.3-4.5	3.5±0.5	3.6±0.6	0.588
Total protein	6.5±0.9	4.9-10.1	6.4±1.0	6.5±0.9	0.300
Lymphocytes	2.4±5.2	0.14-26.7	3.1±6.8	1.8±2.8	0.542
Cancer type, n (%)					0.061
Lymphoma	32 (72.7)		14 (63.6)	18 (81.8)	
Acute myeloid leukemia	8 (18.2)		7 (31.9)	1 (4.5)	
Acute lymphoblastic leukemia	2 (4.5)		0 (0.0)	2 (9.2)	
Multiple myeloma	1 (2.3)		1 (4.5)	0 (0.0)	
Chronic myeloid leukemia	1 (2.3)		0 (0.0)	1 (4.5)	
Days since hospitalization	8.1±9.5	1-47	7.1±6.8	9.2±11.5	0.991
Pre- or post-chemotherapy					
Pre-chemotherapy, n (%)	14 (31.8)		6 (27.2)	8 (36.4)	
Post-chemotherapy, n (%)	30 (68.2)		16 (72.8)	14 (63.6)	
Days since chemotherapy	1.7±8.7	-16-46	1.0±3.9	2.4±11.6	0.813
Hospital stay, days	40.5±23.3	12-130	36.7±21.0	44.3±24.8	0.162
Disease duration, days	667.5±1308.3	2-8083	339.1±451.5	995.8±1733.1	0.231
Intervention frequency		0.38-1.0	0.93±0.06	0.66±0.14	<0.001
Exercise intensity, %	22.3±9.6.		22.5±10.5	22.0±8.2	0.948

BMI: body mass index. CRP: C-reactive protein. Intervention frequency: the value of the number of intervention days divided by the number of weekdays from the initiation of rehabilitation until discharge. Data are presented as mean ± SD.

Table 2. Baseline and post-treatment values (change from baseline to post-treatment in muscle function, physical function, and ADLs)

Parameters	HF group (n=22)				LF group (n=22)				Group× Time
	Baseline (mean±SD)	Post-treatment (mean±SD)	Change from baseline (mean±SD)	Within-group P-value	Baseline (mean±SD)	Post-treatment (mean±SD)	Change from baseline (mean±SD)	Within-group P-value	P-value
Body weight, kg	56.3±13.7	54.6±13.0	-1.7±2.2	0.016	52.5±9.3	49.6±8.2	-2.9±3.8	<0.001	0.232
HS, kgf	24.2±11.4	25.0±11.8	0.8±2.1	0.240	21.5±8.5	21.1±7.8	-0.4±4.0	0.619	0.238
IKES, kgf	27.2±10.4	27.8±10.2	0.7±5.8	0.600	24.3±13.7	21.5±12.9	-2.9±5.7	0.028	0.053
MT, mm	15.9±6.0	15.3±5.6	-0.6±2.6	0.341	14.8±5.2	13.4±4.0	-1.4±3.0	0.025	0.338
10MWT, sec	8.2±2.3	7.1±1.7	-1.2±1.4	0.003	8.8±2.7	8.6±2.7	-0.2±1.7	0.531	0.067
TUGT, sec	10.3±3.4	8.0±1.6	-2.2±2.5	0.210	9.6±3.5	8.9±3.0	-1.2±3.6	0.294	0.123
ECOG PS	2.0±0.8	1.6±0.7	-0.5±0.7	0.001	1.8±0.9	1.8±0.8	0.0±0.6	1.000	0.014
FIM	112.9±16.4	121.8±5.5	9.0±14.9	0.001	120.2±7.2	121.7±4.1	1.5±6.9	0.545	0.045

LF: low-frequency. HF: high-frequency. Baseline: start date of rehabilitation. Post-treatment: discharge. HS: handgrip strength. IKES: isometric knee extensor strength. MT: muscle thickness. 10MWT: 10-meter walk test. TUGT: timed up and go test. ECOG PS: the Eastern Cooperative Oncology Group Performance Status. FIM: Functional Independence Measure. Sample size: MT; HF n=21, LF n=21 (% of missing value of both HF and LF was 4.5). 10MWT; HF n=20 (% of missing value of HF was 9.1). TUGT; HF n=20, LF n=17 (% of missing value of HF and LF were 9.1 and 22.7, respectively).

Table 3. Baseline and post-treatment values (change from baseline to post-treatment in psychological distress)

Parameters	HF group (n=22)				LF group (n=22)				Group×Time
	Baseline (mean±SD)	Post-treatment (mean±SD)	Change from baseline (mean±SD)	Within-group P-value	Baseline (mean±SD)	Post-treatment (mean±SD)	Change from baseline (mean±SD)	Within-group P-value	P-value
HADS									
Total	12.8±5.2	9.7±4.6	-3.2±0.9	0.001	12.3±6.9	10.9±6.0	-1.4±1.0	0.164	0.203
Anxiety	5.8±3.2	3.8±2.7	-2.0±2.7	0.002	6.4±4.8	5.0±3.8	-1.4±2.1	0.044	0.532
Depression	7.0±3.0	5.8±3.4	-1.2±2.5	0.068	5.9±3.9	5.9±3.2	0.0±2.6	1.000	0.220

LF: low-frequency. HF: high-frequency. Baseline: start date of rehabilitation. Post-treatment: discharge. HADS: Hospital Anxiety and Depression Scale. Sample size: HF n=18, LF n=14 (% of missing value of HF and LF were 18.2 and 36.4, respectively).

Table 4. Baseline and post-treatment values (change from baseline to post-treatment in QOL)

Parameters	HF group				LF group				Group×Time
	Baseline (mean±SD)	Post-treatment (mean±SD)	Change from baseline (mean±SD)	Within-group P-value	Baseline (mean±SD)	Post-treatment (mean±SD)	Change from baseline (mean±SD)	Within-group P-value	P-value
Global health	45.8±25.9	61.1±20.8	15.3±23.9	0.019	50.6±23.1	57.1±17.0	6.4±27.2	0.385	0.360
Physical	61.1±19.4	74.4±17.3	13.3±18.1	0.002	82.1±9.6	84.6±14.2	2.6±12.7	0.581	0.085
Role	56.5±30.9	72.2±29.7	15.7±38.7	0.079	85.9±16.5	78.2±31.5	-7.7±30.4	0.455	0.089
Emotional	69.4±23.0	84.3±11.0	14.8±19.4	0.002	72.4±18.1	79.5±21.7	7.1±15.3	0.177	0.255
Cognitive	66.7±29.7	83.3±26.2	16.7±20.0	<0.001	85.9±13.3	84.6±17.3	-1.3±12.2	0.796	0.010
Social	72.2±33.3	83.3±19.8	11.1±30.9	0.101	83.3±19.2	82.1±19.8	-1.3±20.1	0.869	0.231
Nausea/vomiting	6.5±14.2	3.7±9.1	-2.8±13.9	0.379	2.6±6.3	5.1±12.5	2.6±11.0	0.489	0.275
Fatigue	46.9±24.9	32.7±19.6	-14.2±28.6	0.017	29.1±15.4	26.5±8.5	-2.6±11.7	0.701	0.191
Dyspnea	31.5±29.1	20.4±16.7	-11.1±27.2	0.089	17.9±22.0	7.7±14.6	-10.3±24.1	0.178	0.931
Pain	31.5±31.3	15.7±13.7	-15.7±22.5	0.003	15.4±14.4	6.4±8.4	-9.0±15.5	0.127	0.374
Insomnia	51.9±26.1	33.3±16.2	-18.5±25.4	0.013	20.5±21.7	28.2±30.0	7.7±32.4	0.355	0.021
Appetite loss	20.4±28.3	20.4±28.3	0.0±36.9	1.000	20.5±21.7	17.9±17.3	-2.6±15.8	0.767	0.821
Constipation	27.8±20.6	24.1±27.5	-3.7±29.2	0.588	20.5±29.0	25.6±27.7	5.1±25.6	0.524	0.404
Diarrhea	13.0±20.3	11.1±16.2	-1.9±23.5	0.773	17.9±25.9	17.9±29.2	0.0±28.2	1.000	0.852
Financial difficulties	25.9±29.3	18.5±28.5	-7.4±24.1	0.316	20.5±25.6	15.4±22.0	-5.1±31.6	0.553	0.840

LF: low-frequency. HF: high-frequency. Baseline: start date of rehabilitation. Post-treatment: discharge. Sample size: HF=18, LF=13 (% of missing value of HF and LF were 18.2 and 40.9, respectively).