VU VRIJE UNIVERSITEIT AMSTERDAM

VU Research Portal

Physical exercise in patients with hematological malignancies

Knols, R.H.W.

2011

document version
Publisher's PDF, also known as Version of record

Link to publication in VU Research Portal

citation for published version (APA)
Knols, R. H. W. (2011). *Physical exercise in patients with hematological malignancies*.

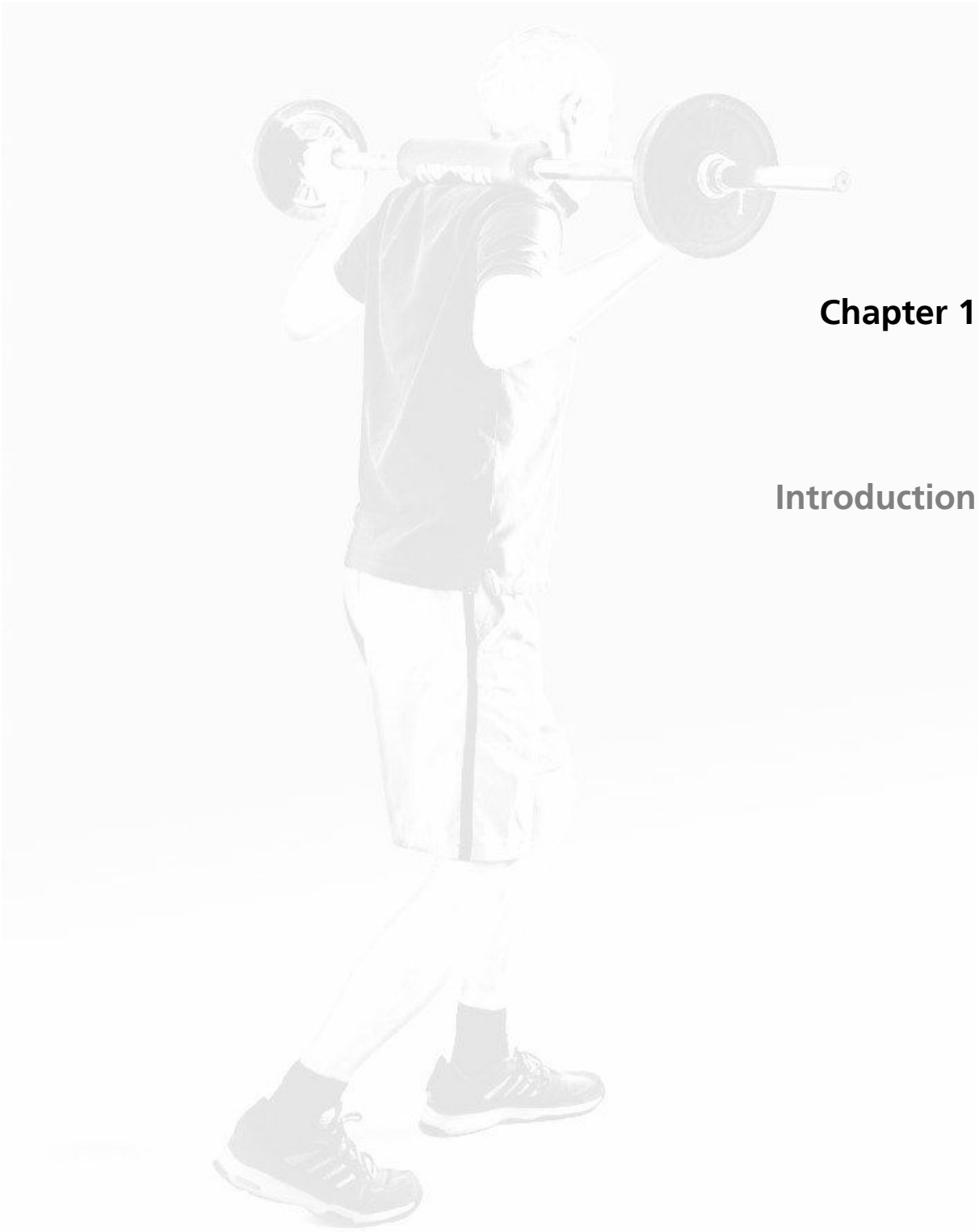
General rights
Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal ?

Take down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

E-mail address:
vuresearchportal.ub@vu.nl

Download date: 26. Oct. 2021



Chapter 1

Introduction

Hematological malignancies

According to the WHO classification of neoplastic diseases of the hematopoietic and lymphoid tissues, hematological malignancies are primarily stratified by their lineage (e.g. myeloid and lymphoid neoplasms, plasma-cell disorders [1]. In 2005, approximately 144,000 new patients were diagnosed with hematological malignancies in the European Economic Area (including Switzerland). These new cases of leukemia, Hodgkin's and non-Hodgkin's lymphoma (NHL) and myeloma account for approximately 11% of all of the new cancer patients diagnosed in Europe, and for approximately 12% of all cancer-related deaths [2].

The American Cancer Society has estimated that approximately 44,790 new cases of leukemia [3], 8,510 new cases of Hodgkin's lymphoma [4], 65,980 new cases of non-Hodgkin's lymphoma [5], and 20,580 new cases of myeloma [6] were diagnosed in the U.S. in 2009. In 2009, it is estimated that there were approximately 21,870 deaths from leukemia [3], 1,290 from Hodgkin's lymphoma [4], 1,950 from non-Hodgkin's lymphoma [5], and 10,580 from multiple myeloma [6].

Treatment of hematological malignancies

There are a number of treatment approaches available for hematological malignancies that can be organized into three categories: induction, consolidation, and maintenance therapy. Stem-cell transplantation (either autologous or allogeneic) is frequently applied. In addition, patients can be treated with monoclonal antibodies or radiotherapy. For several diseases, including early stages of good risk chronic lymphocytic leukemia, and asymptomatic low-grade non-Hodgkin's lymphoma, a wait-and-see (active surveillance) policy can be followed [7-9].

Survival

The overall five year survival rates for hematological malignancies increased from 12% in the 1960s to 34% in 2003 for multiple myeloma, from 40% to 86% for Hodgkin's lymphoma, from 31% to 64% for non-Hodgkin's lymphoma, and from 14% to 50% for leukemia [10].

Side-effects and related problems in the treatment of hematological malignancies

High-dose chemotherapy (HDC) following hematopoietic stem cell transplantation (HSCT) is an intensive cancer therapy that has been commonly used to treat patients with hematological malignancies [11]. Before, during and after HDC and HSCT, patients often experience high levels of both physical and psychological stress. Such stress tends to occur even if medical treatment is successful, and is believed to negatively influence the long-term success of the HSCT procedure [11].

The physical and psychosocial problems that are frequently reported are compromised physical performance and an impaired level of physical functioning [12,13] and physical activity [12,14],

fatigue [12,15], loss of body weight [12,16], immunological / hematological changes [12,17] and psychological distress [12,18]. In addition, common somatic side effects (e.g. graft versus host disease (GVHD), infection, diarrhea, nausea, pain) likely exacerbate physical and psychological problems [11,18]. Other factors such as hospitalization for isolated conditions, side effects of other medications, rapid and unsteady changes in clinical status, and the real risk of dying further lead to treatment-related problems and stress. In this way, physical and psychosocial distress, treatment-related side effects and the disease process itself interact and influence the overall success of the treatment and the well-being of the patient [12]. In the end, all of these physical and psychological problems can have a significant effect on the quality of life of the patient [19,20]. Additionally, patients often experience problems with reintegration into the community following HDC and HSCT, [11] and may not be able to fully fulfill their previous social roles [21].

Cancer rehabilitation in Switzerland

Cancer rehabilitation aims to help patients to achieve maximum physical, social, psychological and vocational functioning within the limits imposed by the disease and its treatment [22]. Cancer patients in Switzerland generally have access to excellent diagnostic and therapeutic treatment procedures. However, contrary to the situation in Anglo-Saxon countries (e.g., the U.S., Australia, Canada), Scandinavia (e.g., Denmark, Norway, Sweden) and a number of countries in Western Europe (e.g., Germany, The Netherlands), Switzerland has relatively few inpatient and outpatient cancer rehabilitation services [23]. The need for more extensive cancer rehabilitation services has been recognized by several important agencies in Switzerland, including the Krebsliga Schweiz, the Bernische Krebsliga and Oncosuisse [23]. Currently, specific cancer rehabilitation programs are available at inpatient treatment facilities such as Braunwald (Ct. Glarus) and Montana (Ct. Valais), and between 40 and 50 outpatient exercise groups are available within the cantonal and regional divisions of the Krebsliga Schweiz.

Physical exercise in cancer patients

Physical exercise (PE) has been demonstrated to improve health outcomes in breast cancer [24], prostate cancer [25], and head and neck cancer patients [26]. PE may be particularly helpful in maintaining or improving physical functioning in cancer patients [24,25]. A recently published meta-analysis showed a large effect of post-treatment physical activity interventions on upper and lower body strength, and moderate effects on fatigue and breast cancer-specific concerns. A small to moderate positive effect of physical activity during treatment has been demonstrated for physical activity level, aerobic fitness, muscular strength, anxiety, self-esteem, and quality of life [27]. With few exceptions, exercise is well tolerated both during and following treatment [27].

Physical exercise in patients with hematological malignancies

Dimeo et al. (1996) [28] were the first to demonstrate the beneficial effects of physical exercise on physical performance and fatigue in hematological cancer patients undergoing bone-marrow transplantation. Several other studies have also reported on the salutary effects of physical exercise both during HDC (and HSCT) and during the rehabilitation phase on physical and psychological outcomes [12, 29-32]. Physical exercise appears to be particularly effective in stabilizing physical performance during the HSCT phase of treatment [12]. Despite these promising findings, however, methodological limitations, including treatment groups in a random and concealed manner, the lack of appropriate control groups, the lack of blinded assessors and failure to provide intention-to-treat analyses suggested the need for further research on the effectiveness of outpatient physical exercise programs on hematological cancer patients during the rehabilitation phase [12,29].

The overall aim of the PhD trajectory was to develop and test the effectiveness of a physical exercise intervention for patients with hematological malignancies during the post-treatment rehabilitation phase in terms of physical endurance and strength, daily walking activity, and health-related quality of life. To achieve this aim, several intermediate research activities/steps were necessary, each of which is reported in separate chapters in this thesis.

Systematic review of physical exercise in cancer patients

The first step in this project was to systematically review the methodological quality of and summarize the evidence from trials examining the effectiveness of physical exercise in improving the level of physical functioning and psychological well being of cancer patients **(chapter 2)**. The effects of physical exercise programs were examined for patients with breast cancer, patients with hematological malignancies and for patients with mixed solid tumors both during and after anti-cancer treatment.

Measurement error

The interpretation of the results of effectiveness studies is traditionally focused on statistical significance rather than on clinical importance. A statistically significant difference between two groups of patients implies that one group of patients has improved or deteriorated more than can be expected by chance alone compared to another group of patients [33,34]. The research question addressed in **chapters 3 and 4** was whether the degree of measurement error of the assessment protocol for the CompuFet hand-held dynamometer and CYMA step activity monitor 3 (SAM3), was small enough to allow one to detect a "real" change between pre- and post-measurements for knee extension strength and daily walking activity. Toward this

end, we calculated the standard error of measurement (SEM), the smallest detectable difference (SDD) and the limits of agreement for these measures.

Walking

Walking is a major component of daily physical activity and the most common form of exercise [35]. Walking can be assessed at an hypothetical level (e.g., by posing questions about functional capacity), an experimental level (e.g., by assessing physical performance), and at the level of enacted functioning e.g., by assessing actual physical activity). In this study, we investigated the associations between measures of daily walking activity over a 7-day period, standardized walking and self-reported physical functioning among hematopoietic stem cell transplantation patients **(chapter 5)**. The aim of this study was to estimate whether these measures are complementary (i.e., add information) or are (partially) redundant. We also compared daily walking activity of patients with hematological malignancies after high-dose chemotherapy to that of healthy subjects **(chapter 4)**.

Development and evaluation of a physical exercise intervention

For the central part of this thesis **(chapter 6)**, we developed and conducted a randomized clinical trial to evaluate the effects of a physical exercise intervention compared to a usual care control group in patients with hematological malignancies who had recently completed HDC and HSCT. The intervention was developed on the basis of information derived from our systematic review [36] and other literature [37-42], and on our clinical experience.
The physical exercise group received a 12-week supervised physical exercise program, containing endurance and resistive strength exercises. The program was performed twice a week in a physiotherapy clinic or fitness centre near the patient's home. Ergometer-cycling or treadmill-walking were used as cardiovascular training. The exercise was designed to maintain aerobic performance for at least 20 minutes at a pre-defined individual heart rate (50%, increasing to 75% of the estimated maximum heart rate) [12]. The intensity of the cardiovascular training was continuously adapted to stay on the training level of the heart rate. Cardiovascular training was combined with progressive resistance training in order to counteract cancer-related decrease in muscle strength [43].

Improvement of walking activity in cancer patients

While patients with cancer may benefit from physical exercise programs, it is unclear, the extent to which short term maintenance or enhancement of physical activity levels are sustained over time. Thus, the last step in this thesis **(chapter 7)** included a systematic review of the literature reporting on the effectiveness of physical activity interventions on daily walking in patients with cancer.

The thesis concludes with a general discussion **(chapter 8)** and a summary in English, Dutch and German.

In summary, the series of studies reported in this thesis addressed the following research questions:

1) Is physical exercise effective in improving physical and psychological health outcomes in (hematological) cancer patients and what is the methodological quality of studies in this area?

2) What is the measurement error associated with outcome measures typically used in assessing the effects of physical exercise programs among patients with hematological malignancies, and is there a difference in walking activity between patients with hematological malignancies and healthy participants?

3) Is there a significant association between self-reported functional capacity, walking performance and enacted walking?

4) Is an outpatient physical exercise intervention following HSCT effective in improving physical and psychological outcomes in patients with hematological malignancies?

5) Can we sustain improvements in walking activity in cancer patients over extended periods of time?

References

1. Harris NL, Jaffe ES, Diebold J, Flandrin G, Muller-Hermelink HK, Vardiman J, Lister TA, Bloomfield CD. World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues: report of the Clinical Advisory Committee meeting-Airlie House, Virginia, November 1997. J Clin Oncol 1999;17: 3835-3849.

2. Boyle P, Ferlay J. Cancer incidence and mortality in Europe, 2004. Ann Oncol 2005;16: 481-488.

3. National Cancer Institute. Leukemia; http://www.cancer.gov/cancertopics/types/leukemia.

4. National Cancer Institute. Lymphoma; http://www.cancer.gov/Templates/db_alpha.aspx?CdrID=45368.

5. http://www.cancer.gov/cancertopics/types/non-hodgkins-lymphoma.

6. National Cancer Institute. Myeloma; http://www.cancer.gov/cancertopics/types/myeloma.

7. Schouten HC. General principles of treatment. Ann Oncol 2007;18 (Suppl 1): 29-32.

8. Attal M, Harousseau J-L, Facon T, Guilhot F, Doyen C, Fuzibet JG, Monconduit M, Hulin C, Caillot D, Bouabdallah R, Voillat L, Sotto JJ, Grosbois B, Bataille R; InterGroupe Francophone du Myélome. Single versus double autologous stem-cell transplantation for multiple myeloma. New Engl J Med 2003;349: 2495-2502.

9. Allogeneic peripheral blood stem-cell compared with bone marrow transplantation in the management of hematologic malignancies: an individual patient data meta-analysis of nine randomized trials. Stem Cell Trialists' Collaborative Group. J Clin Oncol 2005;23: 5074-5087.

10. Ries LAG, Melbert D, Krapcho M, Ries LAG, Melbert D, Krapcho M, Mariotto A, Miller BA, Feuer EJ, Clegg L, Horner MJ, Howlader N, Eisner MP, Reichman M, Edwards BK (eds). SEER Cancer Statistics Review, 1975-2005, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2005/, based on November 2007 SEER data submission, posted to the SEER web site, 2008.

11. Mosher CE, Redd WH, Rini CM, Burkhalter J, Duhamel K. Physical, psychological, and social sequelae following hematopoietic stem cell transplantation: a review of the literature. Psychooncology 2009;18: 113-127.

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

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

14. Oldervoll LM, Loge JH, Kaasa S, Lydersen S, Hjermstad MJ, Thorsen L, Holte H, Jacobsen AB, Fosså SD. Physical activity in Hodgkin's lymphoma survivors with and without chronic fatigue compared with the general population-a cross-sectional study. BMC Cancer 2007;12: 210.

15. Lucía A, Earnest C, Pérez M. Cancer-related fatigue: can exercise physiology assist oncologists? Lancet Oncol 2003;4: 616-625.

16. Hastings Y, White M, Young J. Enteral nutrition and bone marrow transplantation. J Pediatr Oncol Nurs 2006;23: 103-110.
17. Kim SD, Kim HS. A series of bed exercises to improve lymphocyte count in allogeneic bone marrow transplantation patients. Eur J Cancer Care (Engl) 2006;15: 453-457.
18. Neitzert C, Ritvo P, Dancey J, Weiser K, Murray C, Avery J. The psychosocial impact of bone marrow transplantation: a review of the literature. Bone Marrow Transplant 1998;22: 409-422.
19. Hjermstad M, Holte H, Evensen S, Fayers P, Kaasa S. Do patients who are treated with stem cell transplantation have a health-related quality of life comparable to the general population after 1 year? Bone Marrow Transplant 1999;24: 911-918.
20. Hjermstad MJ, Knobel H, Brinch L, Fayers PM, Loge JH, Holte H, Kaasa SA. A prospective study of health-related quality of life, fatigue, anxiety and depression 3-5 years after stem cell transplantation. Bone Marrow Transplant 2004;34: 257-266.
21. Baker F, Zabora J, Polland A, Wingard J. Reintegration after bone marrow transplantation. Cancer Pract 1999;7: 190-197.
22. May A. Rehabilitation in cancer: Training and talking? Effects of physical training versus physical training with cognitive-behavioural therapy. Doctoral thesis, University of Utrecht, The Netherlands, 2008.
23. Eberhard S, Buser K. Rehabilitation bei onkologischen Erkrankungen. Onkologie 2007;3: 45-51.
24. McNeely ML, Campbell KL, Rowe BH, Klassen TP, Mackey JR, Courneya KS. Effects of exercise on breast cancer patients and survivors: a systematic review and meta-analysis. CMAJ 2006;175: 34-41.
25. Thorsen L, Courneya KS, Stevinson C, Fosså SD. A systematic review of physical activity in prostate cancer survivors: outcomes, prevalence, and determinants. Support Care Cancer 2008;16: 987-997.
26. McNeely ML, Parliament MB, Seikaly H, Jha N, Magee DJ, Haykowsky MJ, Courneya KS. Effect of exercise on upper extremity pain and dysfunction in head and neck cancer survivors: a randomized controlled trial. Cancer 2008;113: 214-222.
27. Speck RM, Courneya KS, Mâsse LC, Duval S, Schmitz KH. An update of controlled physical activity trials in cancer survivors: a systematic review and meta-analysis. J Cancer Surviv 2010;4: 87-100.
28. Dimeo F, Bertz H, Finke J, Fetscher S, Mertelsmann R, Keul J. An aerobic exercise program for patients with haematological malignancies after bone marrow transplantation. Bone Marrow Transplant 1996;18: 1157-1160.

29. Liu RD, Chinapaw MJ, Huijgens PC, van Mechelen W. Physical exercise interventions in haematological cancer patients, feasible to conduct but effectiveness to be established: A systematic literature review. Cancer Treat Rev 2009;35: 185-192.
30. Jarden M, Baadsgaard MT, Hovgaard DJ, Boesen E, Adamsen L. A randomized trial on the effect of a multimodal intervention on physical capacity, functional performance and quality of life in adult patients undergoing allogeneic SCT. Bone Marrow Transplant 2009;43: 725-737.
31. Baumann FT, Kraut L, Schüle K, Bloch W, Fauser AA. A controlled randomized study examining the effects of exercise therapy on patients undergoing haematopoietic stem cell transplantation. Bone Marrow Transplant 2010;45: 355-362.
32. Shelton ML, Lee JQ, Morris GS, Massey PR, Kendall DG, Munsell MF, Anderson KO, Simmonds MJ, Giralt SA. A randomized control trial of a supervised versus a self-directed exercise program for allogeneic stem cell transplant patients. Psychooncology 2008;18: 353-359.
33. van der Roer N. Economic evaluations in low back pain. Getting the value back. Doctoral thesis, Vrije Universiteit Amsterdam, The Netherlands, 2006.
34. de Vet HC, Terwee CB, Knol DL, Bouter LM: When to use agreement versus reliability measures. J Clin Epidemiol 2006;59: 1033-1039.
35. Manson JE, Greenland P, LaCroix AZ, Stefanick ML, Mouton CP, Oberman A, Perri MG, Sheps DS, Pettinger MB, Siscovick DS: Walking compared with vigorous exercise for the prevention of cardiovascular events in women. N Engl J Med 2002;347: 716-725.
36. Knols R, Aaronson NK, Uebelhart D, Fransen J, Aufdemkampe G. Physical exercise in cancer patients during and after medical treatment: a systematic review of randomized and controlled clinical trials. J Clin Oncol. 2005;23: 3830-42.
37. Hayes SC, Davies PS, Parker TW, Bashford J, Green A. Role of a mixed type, moderate intensity exercise programme after peripheral blood stem cell transplantation. Br J Sports Med 2004;38: 304-309.
38. Hayes S, Davies PS, Parker T, Bashford J. Total energy expenditure and body composition changes following peripheral blood stem cell transplantation and participation in an exercise programme. Bone Marrow Transplant 2003;31: 331-338.
39. Hayes SC, Rowbottom D, Davies PS, Parker TW, Bashford J. Immunological changes after cancer treatment and participation in an exercise program. Med Sci Sports Exerc 2003;35: 2-9.
40. Hayes S, Davies PS, Parker T, Bashford J, Newman B. Quality of life changes following peripheral blood stem cell transplantation and participation in a mixed-type, moderate-intensity, exercise program. Bone Marrow Transplant 2004;33: 553-558.
41. Coleman EA, Coon S, Hall-Barrow J, Richards K, Gaylor D, Stewart B. Feasibility of exercise during treatment for multiple myeloma. Cancer Nurs 2003;26: 410-419.

42. Dimeo FC, Tilmann MH, Bertz H, Kanz L, Mertelsmann R, Keul J. Aerobic exercise in the rehabilitation of cancer patients after high dose chemotherapy and autologous peripheral stem cell transplantation. Cancer 1997;79: 1717-1722.
43. Oldervoll LM, Kaasa S, Hjermstad MJ, Lund JA, Loge JH. Physical exercise results in the improved subjective well-being of a few or is effective rehabilitation for all cancer patients? Eur J Cancer 2004;40: 951-962.