Physical exercise in patients treated with hematopoietic stem cell transplantation

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General introduction

Hematologic malignancies and hematopoietic stem cell transplantation

Hematologic malignancies are neoplasms of the lymphoid or hematopoietic tissues,[1] of which lymphoma, leukemia and multiple myeloma are amongst the most prevalent disorders. In the Netherlands, over 9000 new patients were diagnosed with a hematologic malignancy in 2016, accounting for 8% of all new cancer cases.[2] The 5-year overall survival rates vary widely per diagnosis, from 20% for acute myeloid leukemia to 85% for patients with Hodgkin's lymphoma (2008–2012).[2]

Hematopoietic stem cell transplantation (HSCT) has favorable effects on survival in patients with various hematologic malignancies when compared to alternative non-transplant treatments.[3,4] The aim of HSCT is usually to cure, or in some malignancies (e.g. multiple myeloma) to improve survival.[3] Two frequently applied types of HSCT can be distinguished: autologous stem cell transplantation (auto-SCT), which uses the patient's own stem cells, and allogeneic stem cell transplantation (allo-SCT), which uses the stem cells of a donor.[5,6] Auto-SCT is currently standard of care for patients aged below 65–70 years with multiple myeloma in first line and in patients with aggressive lymphoma in first or second line.[4,5] Allo-SCT is indicated for acute leukemia and myelodysplastic syndrome in first line and can be used in multiple myeloma, chronic myeloid leukemia and lymphoma in second line or when auto-SCT has failed.[4,5] The number of HSCTs in Europe has increased with 80% when compared with 15 years ago (2000).[7] In the Netherlands in 2015, 516 allo-SCTs and 780 auto-SCTs were performed in patients who were not previously transplanted.[8]

A schematic overview of the auto- and allo-SCT trajectories is presented in Figure 1.1. Auto-SCT enables the use of high-dose chemotherapy, which is needed to eliminate the remaining malignant cells. This high-dose chemotherapy will, however, also cause a partial or complete bone marrow ablation.[5,6] Therefore, earlier in the trajectory, the patient's own stem cells are mobilized and collected. After the administration of the high-dose chemotherapy, the stem cells are reinfused[5,6] in order to restore the normal hematopoiesis.[6]

Allo-SCT uses HLA-matched donor stem cells from family members (usually a brother or sister), unrelated donors or cord blood (HLA = human leucocyte antigens). The regimen given prior to transplant can either be myeloablative or of a reduced intensity, depending mainly on the age and diagnosis of the patient.[5] The mechanism of action of the transplantation is primarily based on the immune response of the donor cells against the 'foreign' residual malignant cells, the so-called graft-versus tumor effect. Unfortunately, the immune response is often also directed against the patient's normal cells, and this graft-versus-host disease (GVHD) may even cause fatal destruction of the normal organ tissues.[5,6]

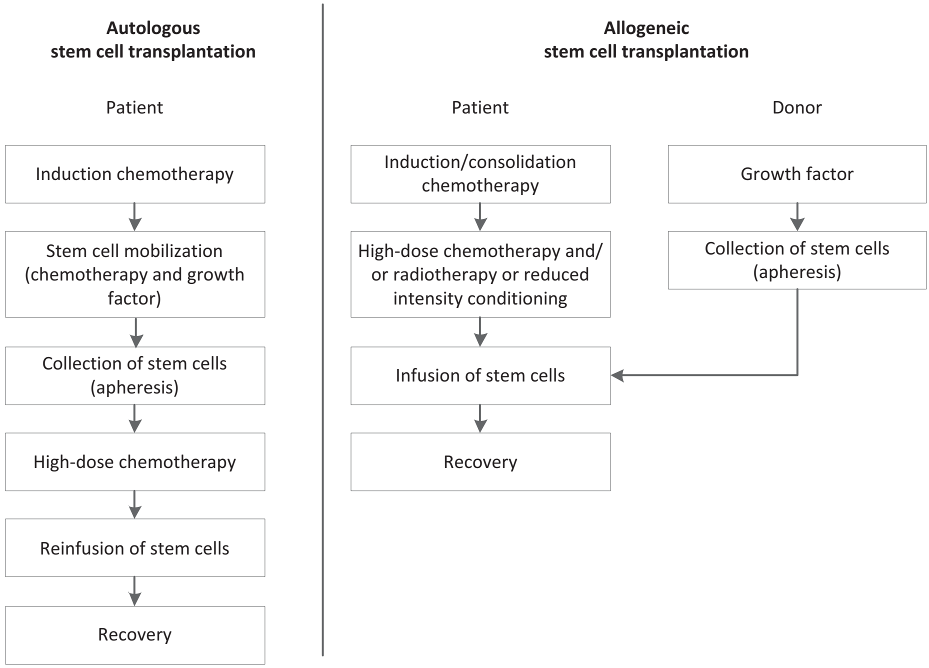

Figure 1.1. Schematic overview of the treatment sequence in autologous and allogeneic stem cell transplantation.
Figure adapted from the Dutch Cancer Society.

Physical and psychological problems during and after HSCT

Although HSCT improves survival, it remains an aggressive treatment option. The transplant-related mortality is less than 5% for auto-SCT, but is substantial for allo-SCT.[3] Factors influencing the outcome after HSCT include age, type and stage of the disease, performance status/ comorbidity at time of the transplant and the degree of HLA mismatch.[3,4] In addition to GVHD in allo-SCT, common medical complications in both auto-SCT and allo-SCT include mucositis and infections in the short term,[3] and secondary cancers and endocrine disorders (including gonadal dysfunction) in the long term.[5,9] Although most HSCT survivors will resume their routine activities,[10] patients may face symptoms as fatigue, distress, sexual dysfunction, musculoskeletal problems, and/or neurocognitive deficits.[9] In a recent cross-sectional study evaluating problems and care needs among Dutch HSCT survivors treated less than 5.5 years ago, patients mainly reported physical problems: 59–70% of the patients treated with allo-SCT and 47–53% of the patients treated with auto-SCT experienced problems with *fatigue, being out of shape and muscle strength*.[11] Given these high percentages, it is important to gain insight in the objective measured deficits in physical fitness after transplantation.

Physical fitness, physical activity and fatigue

It has been hypothesized that reduced physical fitness and physical activity after treatment play a role in the persistent fatigue in cancer patients.[12-14] In the past, patients were often advised to rest and to avoid strenuous activities in order to minimize feelings of fatigue and discomfort. Physical inactivity, however, may further deteriorate the already compromised physical fitness and in this way, a self-perpetuating condition of diminished activity, declined physical fitness and easily induced fatigue may be created. It has been suggested that a physical exercise intervention may break this vicious circle.[12-14]

Physical exercise interventions in patients treated with HSCT

The first preliminary studies evaluating the effects of exercise in patients treated with bone marrow transplantation were published in the late eighties of the previous century.[15,16] A decade later, Dimeo et al.[17] reported significant improvements in physical performance among 20 patients (14 completed the study) who participated in a 6-week walking program starting approximately one month after bone marrow transplantation. Hereafter, the research field expanded gradually. Based on their systematic reviews, both Wiskemann et al.[18] and Liu et al.[19] concluded in 2008 and 2009, respectively, that exercise interventions are feasible in patients treated with HSCT, and both groups reported encouraging results on outcomes such as physical fitness and health-related quality of life (HRQoL). However, these authors also noted the methodological shortcomings of the included studies and expressed the need for methodologically sound randomized controlled trials (RCTs).[18,19] The EXercise Intervention after Stem cell Transplantation (EXIST) RCT was designed to address this research gap, and this thesis presents the design and results of this study. As a part of the Alpe d'HuZes Cancer Rehabilitation (A-CaRe) program,[20] EXIST aimed to evaluate the effectiveness of a high intensity exercise program on physical fitness and fatigue in patients recently treated with auto-SCT.

Return to work experiences

Patients who participated in EXIST visited the AMC or the Sports Medical Advice Center Rotterdam to participate in a sports medical examination. Return to work (RTW) was relatively often a subject of conversation during these assessments, and quite a few patients mentioned difficulties they experienced during the RTW trajectory. However, as RTW emerged as an important topic for the patients participating in EXIST, it was quite surprising that the number of studies focusing on the experiences with RTW after HSCT was limited. Given the distinctive aggressiveness of the HSCT and the higher risks of medical complications and symptoms after HSCT when compared to other cancers treatments,[9] it is unknown whether experiences with RTW from patients with other types of cancer are generalizable to HSCT survivors. We hypothesize that HSCT survivors might experience more and maybe also different difficulties.

Aims and outline of this thesis

This thesis focuses on the rehabilitation of patients recently treated with HSCT, and in particular on the effectiveness of exercise interventions. The five specific aims of this thesis are:

1. To quantify health-related physical fitness in patients recently treated with auto-SCT, and to determine its demographic and clinical correlates;
2. To systematically review the literature on the effectiveness of exercise interventions in comparison to usual care with respect to physical fitness, fatigue and HRQoL in patients treated with HSCT;
3. To determine the effectiveness of a high intensity exercise program on physical fitness and fatigue in patients recently treated with auto-SCT;
4. To evaluate the actual implementation of this exercise program;
5. To explore the experiences with RTW among HSCT survivors.

Chapter 2 describes a cross-sectional study on the cardiorespiratory and muscular fitness and body composition and their demographic and clinical correlates in patients recently treated with auto-SCT. Insight in these variables will facilitate the identification of patients at the greatest need for (exercise) interventions. Chapter 3 presents a systematic review synthesizing the evidence on the effectiveness of exercise interventions in patients treated with HSCT for a hematologic malignancy. Chapter 4, 5 and 6 focus on the EXercise Intervention after STem cell Transplantation (EXIST) study: an RCT to evaluate the effectiveness of a high intensity exercise program on fatigue and physical fitness in patients recently treated with auto-SCT. The design of this trial is presented in chapter 4 and the results are described and discussed in chapter 5. The process evaluation in chapter 6 provides information about implementation of the exercise program, about the patients' and physiotherapists' satisfaction with the intervention, and provides lessons learnt for future multicenter RCTs. Chapter 7 focuses on the experiences with return to work (RTW) after HSCT. Insight in different work perceptions, barriers to RTW, and the possible solutions to improve RTW might help researchers, healthcare professionals and employers to develop and/or tailor RTW interventions. In chapter 8 the main findings of this thesis are discussed. Furthermore, the clinical implications and recommendations for future research are presented.

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