Physical exercise in patients treated with hematopoietic stem cell transplantation
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General discussion
This thesis focused on the rehabilitation of patients recently treated with hematopoietic stem cell transplantation (HSCT), and in particular on the effectiveness of exercise interventions in this group of patients. After a short introduction in chapter 1, the following topics were addressed in this thesis: 1) health-related physical fitness after autologous stem cell transplantation (auto-SCT) and its demographic and clinical correlates; 2) effectiveness of exercise interventions compared to usual care, specifically the effectiveness of a supervised high intensity exercise program on physical fitness and fatigue in patients treated with auto-SCT; 4) the implementation of this supervised exercise program; and 5) HSCT survivors’ work perceptions, barriers to and facilitators of return to work (RTW) and possible solutions to improve RTW. In this final chapter the main findings are critically discussed, and the clinical implications and recommendations for future research are presented.

Discussion on the main findings

Cardiorespiratory fitness

Health-related physical fitness of patients recently treated with auto-SCT, and specifically cardiorespiratory fitness, was reduced compared to age- and gender-specific predicted values (chapter 2). After the 18-week exercise program or at a similar time point for the patients in the control group, the average VO$_{2peak}$ values of the patients participating in the EXIST study were still poor: 26.0 mL/kg/min in the intervention group and 24.2 mL/kg/min in the control group (chapter 5). Although our results should be interpreted with caution given that 36% had missing values at follow-up, these values were only slightly lower than those reported in a recent study (27.5 mL/kg/min) among 194 Norwegian lymphoma survivors who were on average 10.2 years post auto-SCT. In this study, physical activity was positively associated with VO$_{2peak}$, and the VO$_{2peak}$ levels of highly active patients were similar to those of a sedentary, healthy reference population. Further longitudinal studies in HSCT survivors are needed to give insight in the course and factors that influence cardiorespiratory fitness in the long term.

Systematic review and meta-analysis

The results of our meta-analysis suggest that exercise has beneficial effects on physical fitness, HRQoL and fatigue when compared to usual care in patients treated with HSCT. Although the inclusion of a meta-analysis in our systematic review can be considered a strength, there was substantial heterogeneity in the effect sizes for cardiorespiratory fitness and lower muscle strength. This may be explained by the considerable variation in clinical characteristics of the patients included, the timing and content of the evaluated interventions, and the outcome measures used across the included studies. The decision whether or not the studies were
homogeneous enough to allow pooling of the data is therefore subject for discussion. Still, given the objective of our review (i.e. to determine the effectiveness of exercise interventions when compared to usual care), we believe it was appropriate to pool the results of the included studies. Although the findings of the meta-analyses are encouraging, the results of our systematic review emphasized the need for additional high quality studies to confirm the potential beneficial effects of exercise interventions in patients treated with HSCT, and when proven effective, to enable the determination of the optimal exercise prescription.

The EXIST study

The EXercise Intervention after Stem cell Transplantation (EXIST) study was a well-designed RCT in which a relatively large and homogeneous group of patients participated and well-accepted outcome measures were used. In contrast to our hypothesis, however, the EXIST intervention had no significant beneficial effects on physical fitness and fatigue levels when compared to usual care. The lack of beneficial effects with respect to fatigue and the majority of the HRQoL scales was in line with the findings of a previous study evaluating the effectiveness of an outpatient exercise program in HSCT survivors. As a previous review reported favorable effects of exercise during hospitalization for allogeneic SCT (allo-SCT) at the moment of discharge from the hospital, it might be that timing of the intervention influences its effectiveness. Exercise might be unable to sufficiently accelerate the natural recovery after recent HSCT (chapter 5). In addition to the potential suboptimal timing of the intervention delivery, the contamination in the control group and/or suboptimal compliance to the prescribed exercise intervention may have diluted potential intervention effects (chapter 5). Unfortunately, these explanations could not be endorsed or falsified by the results of our post hoc analyses (chapter 5) and the process evaluation (chapter 6).

Despite the solid design of the study and the inclusion of a descriptive process evaluation to provide more insight in the implementation quality of the intervention, there are some methodological considerations concerning the study design, study sample, and intervention design and implementation that need to be addressed.

EXIST study – Study design

EXIST included a usual care control condition. At the time the study was designed, exercise after hospitalization was not part of usual care in most transplant centers, although HSCT survivors could participate in a rehabilitation program (Herstel en Balans or a comparable program) in various locations in the Netherlands. We assumed that contrast between our intervention group and our control condition was sufficient, as we expected that only 10–20%
of the patients in the usual care control group would participate in this rehabilitation program. Restricting patients allocated to the control group from physical activity/rehabilitation programs was deemed unethical. However, usual care changed rapidly toward a better accessibility of, and more attention towards cancer rehabilitation: our trial started in the same year the first version of the Dutch guideline on cancer rehabilitation was published (2011), and supervised training options became more widely available. These changes, together with the likelihood that study participants were those already highly motivated to exercise, may have contributed to contamination in the control group.

A different control condition could have resulted in a lower contamination rate. In their systematic review, Steins Bisschop et al. concluded that control groups that are offered an intervention during the study period (e.g. education or regular phone calls) and after the study period (e.g. cross-over study or exercise prescription) have lower contamination and dropout rates. This might explain the difference in contamination rates between the EXIST study and the simultaneously performed Resistance and Endurance exercise After ChemoTherapy (REACT) study, which, like EXIST, was part of the Alpe d’HuZes Cancer Rehabilitation (A-CaRe) program. In REACT the effectiveness of a high intensity and a low-to-moderate intensity exercise intervention were compared with a waiting list control (WLC) group in patients who completed chemotherapy. Only 8% in the WLC group started with supervised exercise at their own initiative. It should be noted, however, that most study designs have weaknesses. Patients in a WLC group may believe that the absence of treatment equals the absence of effects, and these patients may thus improve less than they would normally do. A further disadvantage of a WLC group is that it dismisses the possibility to evaluate long-term effectiveness and cost-effectiveness of interventions.

Recently, Kuehl et al. also reported a high contamination rate (54%) for a control condition in which patients received a muscle relaxation program including supervised sessions during hospitalization for allo-SCT, and a home-based program thereafter. This study used data of the Physical Exercise Training versus Relaxation in Allogeneic stem cell transplantation (PETRA) study, and the reported contamination rate denotes the percentage of patients that reported to perform some kind of sport activity at 180 days post allo-SCT. The results of this study suggest that problems with contamination in exercise trials among HSCT survivors are currently more common.

EXIST study – Study sample

With 109 patients, EXIST is one of the largest studies evaluating the effectiveness of exercise in patients treated with auto-SCT. However, due to slow recruitment and limited options to
further extend the recruitment period and/or the number of participating transplant centers, the target sample size of 120 patients was not reached. Fortunately, study attrition was low (11–15% dropout versus the anticipated 30%; chapter 4), minimizing the loss in statistical power.

There were several reasons for the lower than anticipated recruitment rates: first, the number of eligible patients was less than expected as the recruitment period of EXIST coincided with the recruitment period of a nationwide study in which half of the patients with multiple myeloma were no longer treated with auto-SCT in first line. Second, the opening of the study had to be postponed in two transplant centers until a competitive study was closed. Third, we had anticipated a higher response rate (>50%) than realized.

Given the small and probably clinically irrelevant effect sizes, we do not expect that a larger sample size would have changed the main conclusions. A strength of the EXIST study was that patients were recruited from nine of the thirteen transplant centers in the Netherlands, and the referral areas at these centers included both urban and rural areas. Still, with 34–49% of the eligible patients participating (the exact response rate cannot be calculated as the reasons for not participating were unknown for 97 patients), the sample may have been selective. Patients willing to participate in exercise trials are likely those patients who are already interested in exercise. Previous research groups have identified differences between participants and a subsample of nonparticipants who agreed to fill out a one-time survey.10-12 For instance, the participants in the REACT study were more likely higher educated, non-smokers, and had more often lower psychological distress, higher outcome expectations and perceived more exercise barriers than nonparticipants.11

As a consequence of the slower recruitment, some of the research questions remain unanswered. For instance, the long-term effects, including the effects of exercise on bone mineral density, RTW and costs, have not yet been (fully) analyzed. Unfortunately, slow and/or incomplete recruitment in multicenter RCTs is common.13 A more conservative prognosis of the recruitment rate in combination with more realistic long-term planning will likely increase the probability to successfully complete a study in a reasonable timeframe.

**EXIST study – Intervention design and implementation**

The intervention used in the EXIST study was previously tested by de Backer et al.14,15 in patients treated with chemotherapy with a curative intent. We were able to deliver the program in a physiotherapy practice with basic training facilities close to the patient’s home or work address (mean distance = 2.6 km; chapter 6). It was deemed important to minimize the travel distance, as it has been identified as a barrier for study participation,10,12 and as we expected that a part
of our study sample would have problems with mobility. In addition to deconditioning and anemia, patients with multiple myeloma might for instance suffer from neuropathy due to the use of neurotoxic drugs and the disease itself, and from bone pain and bone fractures due to osteolytic lesions. The downside of this restricted travel distance was that we needed to include and instruct a large number of physiotherapists, and this might have contributed to the variations in training equipment, intervention delivery and/or reporting described in chapter 6.

It is questionable whether two times eight minutes cycling interval training provides a sufficient training load to optimally improve cardiorespiratory fitness. In the REACT study one of the interval training blocks was, from week five onwards, substituted by three bouts of five minutes cycling at a constant workload with one minute rest in between the bouts. Because we did not want to extend the duration of the training sessions, and as the intervention had been proven feasible in previous studies, we decided not to change interval training. Despite these concerns, there were indications that the interval training in the EXIST intervention was too challenging (chapter 6). As also only 47% of the patients participating in the REACT study performed ≥90% of the endurance exercises at the prescribed dose, there seems to be room for improvement of the endurance training component.

Strengths of the exercise intervention include the method to ensure overload and training progression, two important principles of exercise training that were not always implemented in previous interventions. Another strength was that patients and physiotherapists participating in the EXIST intervention were satisfied with the intervention program. Nevertheless, lack of a complete picture of the adherence rates (dose delivered and received) is a limitation. Although the process evaluation was planned in advance, the exercise dose delivered and received of the EXIST intervention could not be fully determined due to the lack of detailed information concerning the performed interval training, and due to the considerable variation in the performance of two resistances exercises (lunges and either sit-ups or abdominal crunches; chapter 6).

Directions for clinical practice and future research

Based on the results of the EXIST study and our qualitative study, the current literature and the evidence-based Dutch guideline on cancer rehabilitation, the following clinical implications and directions for future research can be considered.

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1 The Dutch guideline ‘Cancer Rehabilitation’ is currently being revised, and will likely be replaced/extended by the guideline ‘Medisch specialistische revalidatie bij oncologie’ at the end of 2017.
Clinical implications

As we found no significant beneficial effects of the high intensity supervised exercise program on physical fitness and fatigue in patients recently treated with auto-SCT when compared to usual care, we do not recommend to implement this specific exercise intervention at this specific time point in the treatment trajectory. Yet, the general advantages of regular physical activity are widely recognized. Therefore, patients with hematologic malignancies who do not have medical contra-indications should be recommended to follow the current physical activity guidelines for cancer survivors, which are roughly similar to those for healthy adults.

A substantial part of the HSCT survivors may be able to maintain a physically active lifestyle by themselves. HSCT survivors who would like to participate in moderate or vigorous physical exercise may be advised to undergo a cardiopulmonary exercise test (CPET) to obtain pre-exercise medical clearance (see below). Furthermore, those with musculoskeletal problems (i.e. bone lesions) may need to consult a sports physician, orthopedic surgeon, or physiotherapist in advance to rule out contra-indications for certain types of exercises. Some patients, however, may additionally need to participate in a (partly) supervised exercise program before being able to (safely) comply with the physical activity guidelines on their own. This may specifically concern patients at risk for fractures due to osteolytic bone lesions, patients with fractures and/or cardiovascular disease. According to the current guideline, the primary care providers (e.g. hematologists, nurses, physiotherapists) are responsible for identifying the patients’ care needs/complaints and, when necessary, for referral of patients to monodisciplinary treatments, multidisciplinary rehabilitation treatment or rehabilitation medicine.4

There is some discussion on whether a cardiopulmonary exercise test (CPET) should be conducted in order to provide pre-exercise medical clearance. On the one hand it is of importance to avoid unnecessary barriers to exercise participation, but on the other hand it is also important that exercise is safe. Of the 109 patients participating in EXIST, eight (7%) had to be referred to a cardiologist because of abnormalities during or after the CPET. Apart from one patient with myocardial amyloid deposition without functional implications, no underlying cardiovascular disease was found and all patients received medical clearance for study participation (chapter 2). The eight serious adverse events (four in each group) were considered not to be related to the exercise intervention (chapter 5). This small number of patients with adverse events is, however, clearly insufficient to draw definite conclusions about the safety of exercise and the necessity to perform a CPET. The current guideline refers to the screening recommendations proposed by the American College of Sports Medicine,2

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2 The recommendations for exercise participation health screening have recently been revised. Whether medical clearance is advised is dependent on current physical activity level, presence of signs or symptoms and/or known cardiovascular, metabolic or renal disease, and desired exercise intensity.
and suggests that for instance also severe unexplained fatigue/weakness, and cardiovascular or lung complications due to cancer or its treatment may be indications to perform a CPET. Additional longitudinal research with larger sample sizes is warranted to further elucidate which patients should participate in a CPET before participating in more vigorous forms of exercise.

**Directions for future research**

In addition to the previously mentioned research gaps, future studies should clarify whether exercise interventions that are delivered at a different time point in the treatment trajectory are effective; whether physical fitness and physical exercise are associated with survival in patients recently treated with HSCT; and whether exercise interventions are cost-effective.

As previously described, it might be that a suboptimal timing of the intervention has played a role in the lack of significant favorable effects of exercise on fatigue and HRQoL in the EXIST study. Exercise may not be able to speed up natural recovery after HSCT (chapter 5). An exercise intervention starting during treatment or interventions provided to HSCT survivors with deficits in physical fitness >1 year after transplant might be more beneficial. As studies reported low VO$_{2peak}$ values and muscle strength before transplant, it may be beneficial to start exercising directly after or even during the induction or consolidation chemotherapy and to continue until after the HSCT. RCTs including such a long intervention period are currently lacking.

Interestingly, two recent feasibility studies suggested that pre-transplant VO$_{2peak}$ may predict survival/mortality after allo-SCT. Furthermore, Wiskemann et al. reported encouraging results of an exercise intervention prior to, during and after allo-SCT with respect to survival after hospital discharge. Confirmation of these findings in well-designed and sufficiently powered prospective cohorts and/or randomized trials are highly warranted. Of note, the PETRA study currently evaluates the effects of a year-long partly supervised exercise intervention during and after allo-SCT on 2-year post-SCT survival in 256 patients.

In addition to survival, return to work is an important outcome in patients of working age. The relevance of (return to) work was confirmed in the qualitative study described in chapter 6. RTW after HSCT is often difficult, and there seems to be a need for RTW support. Unfortunately, RTW research among HSCT survivors is in its infancy. Future exercise/rehabilitation trials are recommended to include RTW as outcome or consider including vocational counselling in their intervention programs, as participation in multidisciplinary interventions seems to lead to higher RTW rates. When vocational counselling is included, it seems important that counselling is tailored to the individual work perceptions (chapter 6).
It is important that the exercise trials are accompanied by process evaluations and cost-effectiveness analyses. The importance of performing process evaluations and specifically the reporting of the dose delivered and received is discussed previously in chapter 6. In short, process evaluations provide information about the implementation of the intervention and may help to explain why an intervention was effective or not. Cost-effectiveness analyses are important as well, as they provide decision makers with the information necessary to make decisions on how to allocate the limited health-care resources. Currently, no cost-effectiveness analyses have been performed alongside exercise RCTs in patients treated with HSCT, but some studies have evaluated the cost-effectiveness of exercise interventions in patients with other cancer diagnoses, showing variable results. The analyses of the long-term effectiveness (including the analyses for bone mineral density, return to work and cost-effectiveness) of the EXIST study still have to be performed or finalized. Although the intervention and usual care was just as effective as usual care on physical fitness and fatigue at first follow-up, it is still possible that the intervention program results in lower costs (i.e. usual care might have been more expensive than usual care) or other long-term benefits.

There are some points of attention for future exercise trials in patients with HSCT. First, as described previously, contamination is a considerable challenge. Exercise is becoming standard of care; patients hospitalized for HSCT are nowadays stimulated to remain active, and the contamination rate in the EXIST (chapter 5) and PETRA study suggest that exercise after HSCT has indeed become more common. It is likely that this trend will continue, and researchers should consider the risk of high contamination when designing control conditions. In addition, the developments in the field of oncology and hematology are going fast. It is likely that new treatment options will emerge over time which may obviate the need for high-dose chemotherapy. With these developments, also the supportive care needs of patients with hematologic malignancies might change.

Concluding remarks

In contrast to our hypothesis and the results of our meta-analysis, the high intensity supervised exercise intervention evaluated in this thesis did not result in significantly improved physical fitness or declined fatigue levels compared to usual care. Unfortunately, we could not definitively determine the reason(s) for the lack of intervention effects. As this thesis also recognized the need for physical and vocational rehabilitation (chapter 2, chapter 7, respectively), we recommend future researchers to focus further on the optimal rehabilitation of patients treated with HSCT for a hematologic malignancy. Future studies may concentrate on exercise interventions at different time points in the treatment trajectory, and also on survival and RTW as outcome measures. Further, we recommend that RCTs are complemented with cost-effectiveness analyses and process evaluations.
References


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