Cancer Treatment Reviews 39 (2013) 682–690

Contents lists available at SciVerse ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevierhealth.com/journals/ctrv

Effects of exercise in patients treated with stem cell transplantation for a hematologic malignancy: A systematic review and meta-analysis

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ARTICLE INFO

Article history:
Received 10 September 2012
Received in revised form 9 January 2013
Accepted 12 January 2013

Keywords:
Physical exercise
Stem cell transplantation
Physical fitness
Fatigue
Quality of life

ABSTRACT

We performed a systematic review and meta-analysis evaluating the effectiveness of exercise interventions compared with usual care on physical fitness, fatigue and health-related quality of life in patients with hematologic malignancies treated with stem cell transplantation. Electronic databases were searched up to June 2012. We included randomized controlled trials comparing exercise with usual care, in which at least 75% of the patients had a hematologic malignancy. Standard mean differences were calculated and pooled to generate summary effect sizes (ES) and 95% confidence intervals (CI). The Cochrane Collaboration Risk of Bias Tool was used to assess the methodological quality of the studies.

Eight studies met our inclusion criteria. Exercise had a statistically significant moderately favourable effect on cardiorespiratory fitness (ES = 0.53, 95% CI = 0.13–0.94), lower extremity muscle strength (ES = 0.56, 95% CI = 0.18–0.94) and fatigue (ES = 0.53, 95% CI = 0.27–0.79). Significant small positive effects were found for upper extremity muscle strength, global quality of life, and physical, emotional and cognitive functioning. In conclusion, exercise seems to have beneficial effects in patients treated with stem cell transplantation. However, all studies had at least some risk of bias, and for cardiorespiratory fitness and lower extremity muscle strength substantial heterogeneity in effect sizes were observed. Further high quality research is needed to determine the optimal exercise intervention and clinical implications.

Introduction

Autologous stem cell transplantation (Auto-SCT) is standard of care for patients with multiple myeloma in first line, and for patients with Hodgkin lymphoma and aggressive non-Hodgkin's lymphoma at first relapse. The transplant-related mortality is below 5%. Allogeneic stem cell transplantation (Allo-SCT) can improve outcome in patients with standard or high risk acute myeloid leukaemia or acute lymphoblastic leukaemia. However, in 15–20% of cases complications such as graft-versus-host disease and infections lead to transplant-related mortality. Currently, the five year event-free survival for the hematologic malignancies most often treated with stem cell transplantation (SCT) ranges from 5–80%.[1] With 50,000 SCTs performed annually worldwide,[2,3] the number of SCT survivors increases rapidly.

Despite advances in supportive care, SCT is still associated with serious morbidity. In addition to graft-versus-host disease and infections, short term complications include nausea, diarrhea, mucositis, pain, anxiety and depression.[4] Although most survivors recover adequately from treatment, a substantial proportion continues to experience psychosocial and/or physical long-term and late effects that reduce health-related quality of life (HRQoL).[5] One of the most prevalent and disturbing long term problems is fatigue.[6–9]

It is hypothesized that persistent fatigue reflects a self-perpetuating condition: cancer, its treatment and the associated bed rest lead to poor physical fitness. As a result, greater effort is required to fulfil the activities of daily living, and performance of these

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http://dx.doi.org/10.1016/j.ctrv.2013.01.001

activities can induce abnormally high levels of fatigue. In order to minimize fatigue, patients will limit their physical activities, which will eventually lead to an even greater decline in physical fitness. An exercise intervention might reverse this downward sequence.[10–14] Currently, the American College of Sports Medicine states that for certain cancer survivor groups, exercise training is safe and results in improved physical functioning and HRQoL, and reduced fatigue.[15] However, the effectiveness of exercise interventions in patients during or after SCT has not yet been fully established. Liu et al.[16] and Wiskemann et al.[17] concluded in their systematic reviews that exercise has positive effects on physical fitness, HRQoL and psychological well-being, but that this evidence is based on studies of low methodological quality. In a more recent review, Wolin et al.[18] concluded that physical activity for adult SCT patients has numerous potential benefits, but they only found weak evidence (defined as $\geqslant$3 high-quality studies, but <75% reporting a significant benefit) for a beneficial effect of exercise on physical fitness, fatigue, and HRQoL.

The field of cancer rehabilitation expands rapidly. More studies with larger sample sizes on the effectiveness of exercise during or after SCT have been published since Wolin et al.,[18] which warrants a new systematic review of the present evidence. Furthermore, the increasing number of published studies allows us to apply stricter in- and exclusion criteria concerning study design and study populations in order to reduce heterogeneity. Hence, the objective of the current review is to systematically review the evidence on effectiveness of exercise interventions in comparison to usual care with respect to physical fitness, fatigue and HRQoL in patients treated with SCT for a hematologic malignancy.

Methods

Database search

A clinical librarian performed a database search in Pubmed, EMBASE, PsycINFO, CINAHL, PeDro and the Cochrane Library up to November 2011. The search was updated in June 2012. The following search terms were used: stem cell transplantation OR stem cell transplant* OR hematopoietic SCT OR hsct OR bone marrow transplant* OR leukemia OR lymphoma OR myeloma OR hematologic neoplasm OR hematologic malignanc* and exercise therapies OR physiotherap* OR exercise tests OR physical therapy OR physical therapies OR physical activit* OR exercises OR aerobic OR aerobics OR training[tw] OR endurance OR strength. Two authors (SP and KW) also searched the reference list of relevant studies and reviews for additional articles.

Inclusion criteria

A study was included if: (1) it was a randomized controlled trial (RCT) published in a peer reviewed journal; (2) the study sample contained at least 75% adult ($\geqslant$18 years) patients treated with SCT for a hematologic malignancy; (3) the outcome measures included cardiorespiratory fitness, upper and/or lower extremity muscle strength, fatigue and/or HRQoL measured with a validated multi-item instrument; (4) the intervention consisted of a physical exercise program or a multi-modal intervention aiming to maintain or improve aerobic capacity and/or muscle strength, while the control condition consisted of usual care; (5) it was a full-text article; (6) it was published in English.

Study selection and data extraction

SP and KW independently reviewed the titles and abstracts of the references retrieved from the literature search. Next, the full text versions of potentially relevant articles were retrieved and checked by the two authors on eligibility. Disagreements were solved by consensus or when necessary, by a third author (MC). Hereafter, SP and KW separately extracted the general study information, the details of the exercise intervention, the number of patients, the results and information about adverse events from every study using a standardized data extraction form. We contacted the authors of the studies in case of missing results. Based on the article of Campbell et al.[19] SP evaluated whether or not the included studies had applied the well established principles of exercise training. These principles include *specificity* (intervention given is based on the primary outcome), *progression* (the program was progressive and training progression was outlined), *overload* (the program was of sufficient intensity/exercise prescribed relative to baseline fitness), *initial values* (selected population has low levels of primary outcome measure and/or baseline physical activity levels), *reversibility* (inactivity after completion of the intervention leads to diminished results at follow-up measures) and *diminishing returns* (when patients keep exercising after completing of the intervention, increasing effort is required for further improvement).

Methodological quality

SP and MC assessed the risk of bias in the included studies using the Cochrane Collaboration Risk of Bias Tool.[20] This tool is a domain-based evaluation in which the domains are considered separately.[20] In this study we focussed on the following domains: randomization sequence generation, allocation concealment, blinding (for participants, intervention administrators and outcome assessors), completeness of outcome data (missing outcome data and intention-to-treat analysis), selective outcome reporting and other sources of bias. Each domain was rated as '+' (low risk of bias), '−' (high risk of bias), or '?' (uncertain risk of bias). Differences in the authors' ratings were resolved by consensus.

Data synthesis and analysis

We performed a meta-analysis if at least two studies had measured the same outcome. In such cases, for each study we calculated the standard mean difference (SMD) to quantify the size of the intervention effect, taking into account the variety of instruments and scales available for similar outcomes. The SMD signifies a difference in mean outcome between the post intervention scores of the intervention and usual care group divided by the pooled standard deviation of the outcome.[20] An SMD of 0.5 thus indicates that the mean of the experimental group is half a standard deviation larger than the mean of the usual care group. Heterogeneity between studies was quantified using the I^2 test, with $I^2 > 50\%$ representing considerable heterogeneity.[20] In addition, we calculated the Q statistic. If the Q value is significant, the null hypothesis of homogeneity is rejected. Since we expected considerable heterogeneity, we chose to perform random effects analysis using the DerSimonian and Laird method. This model assumes that the included studies are drawn from 'populations' of studies that systematically differ from each other.[21] Small, moderate and large effects are defined as effect estimates of 0.2, 0.5 and 0.8, respectively.[22] Data from the time point that directly followed the completion of the intervention were selected for analysis. Individual effect sizes were pooled using Review Manager 5.1.[23]

Results

Study, participant and intervention characteristics

The searches in Pubmed, EMBASE, PsycINFO, CinAhl, PeDro and the Cochrane Library resulted in 6877 papers. One additional