Bone Marrow Transplantation (2010) 45, 217–218

www.nature.com/bmt

EDITORIAL

Can a modest exercise program really improve physical functioning and quality of life among recipients of hematopoietic SCT?

Bone Marrow Transplantation (2010) **45,** 217–218; doi:10.1038/bmt.2009.164

The short- and long-term physical and psychosocial sequelae of hematopoietic SCT (HSCT) have been extensively documented. HSCT has a range of well-recognized acute conditioning-related toxicities (for example, GVHD, nausea and emesis, infections, bleeding), as well as less conspicuous but nonetheless serious effects on general physical capacity or fitness, fatigue, and emotional and social well-being. Since the mid 1990s, researchers have investigated the impact of physical exercise interventions on these outcomes. Exercise has been proposed as a means to help individuals treated with HSCT recover from the deconditioning and the associated loss of functional capacity and debilitating fatigue that can occur with prolonged lack of physical activity.[1,2]

In their 2008 review, Wiskemann and Huber[3] identified 15 studies of physical exercise in the HSCT population. The 15 studies varied in design (randomized controlled trial vs quasi-experimental), intervention (endurance training vs resistance training), setting (inpatient vs outpatient or home-based) and duration (5 weeks to 12 months). Several of the studies reported modest benefits of exercise interventions on endurance, strength, and/or quality of life outcomes. However, the studies have generally been methodologically weak. Among the limitations, five of the 15 studies lacked a no-intervention comparison group and 10 of the studies reported data on 35 or fewer patients who completed the study.

The need for larger randomized controlled trials of exercise interventions in persons treated with HSCT is apparent.[4] In this regard, Jarden *et al.*[5] recently reported the results of a randomized trial of a multimodal, supervised exercise program in adult recipients of allogeneic HSCT. The intervention, which began on the day of admission and spanned the hospitalization period, consisted of exercise, including stationary cycling, resistance training, and dynamic and stretching exercises; and progressive muscle relaxation training and psychoeducation. Jarden *et al.*[5] observed statistically significant effects of the intervention on physical capacity (VO_2 max and muscle strength), functional performance, severity of diarrhea, and days of parenteral nutrition. There were no statistically significant effects on quality of life, fatigue, physical activity levels, or psychological well-being.

In this issue of *Bone Marrow Transplantation*, Baumann *et al.*[6] report on a randomized controlled trial of the effects of supervised exercise therapy on endurance, strength, quality of life (primary outcomes), and on hematopoietic parameters and lung function (secondary outcomes) in 64 patients undergoing either allogeneic or autologous HSCT. Patients in the treatment group received exercise training, including both therapeutic ADL (activities of daily living) training and aerobic endurance training, from the conditioning phase of HSCT until discharge from the hospital. Patients in the control group received the hospital's standard mobilization program. Both groups of patients were attended by a professional therapist. Baumann *et al.*[6] found statistically significant effects of their intervention on strength, endurance, lung function, global quality of life, and the physical functioning subscale of the EORTC QLQ-C30 instrument.

Baumann *et al.*[6] provide intriguing evidence for the effects of a structured exercise intervention on important outcomes in the HSCT setting. We applaud this and similar efforts to systematically evaluate a program of exercise among HSCT patients. Although most centers in the United States encourage increased physical activity among HSCT patients, relatively few centers have formal programs in place to support patients in this respect. Patients are generally instructed to 'stay active,' 'walk around', or 'exert yourself' over the course of HSCT, but this vague advice should not be considered equivalent to a systematic exercise program. Research on structured exercise programs can help guide transplant centers' efforts to offer more concrete and evidence-based direction to their HSCT patients. Issues of deconditioning and fatigue have become even more important to address with the steady rise in the median age of transplant recipients; more patients are entering transplant with a greater number of comorbid conditions and functional limitations.

The intervention tested by Baumann *et al.*[6] offers a potential model for other randomized controlled trials of exercise in the HSCT setting. The ADL training and aerobic training appear to have been moderate in intensity and not unduly complex to implement. That said, the requirement for close monitoring of the aerobic training portion of the training by a professional therapist (for example, '…the WHO-endurance test…was carried out by increasing the load by 25 Watts every 2 min, up to a heart rate of 180 min the patient's age'), makes the exercise intervention less portable to real-world vs research transplantation settings. Clinical research on exercise understandably attempts to standardize both the type and the intensity of the intervention to be able to demonstrate powerful and reproducible effects; to that end, this research may evaluate artificial or exaggerated interventions.

Ideally, an in-patient exercise program would be easily administered, and preferably self-administered, after some initial instruction; it should also require minimal reinforcement from a professional and require no special and expensive equipment. The need for simple and self-administered exercises cannot be overstated. Although transplant centers have moved away from strict patient isolation, concerns persist about minimizing exposures for immunocompromised patients. In-patient settings may lack exercise rooms and thus patients would need to be transported to physical therapy. Outpatient transplant facilities are also not designed for physical exercise. Finally, many patients are quite ill and unable to participate in the standard exercise. Arguably, these are the patients for whom deconditioning is most problematic. A graded exercise routine based on functional ability would be needed for these patients.

The results of available randomized controlled trials in the HSCT population suggest that exercise interventions can have an important function in maintaining or enhancing physical functioning and quality of life after this often-debilitating therapy. The observed effects from these trials are relatively impressive given the generally small numbers of patients included in the work conducted to date. It almost goes without saying, however, that much larger, hypothesis-driven trials are needed to confirm and help explain the benefits suggested by existing trials, and to permit the eventual translation of this research into clinical practice.

These studies should be guided by *a priori* statistical power calculations[7] and explicit definition of clinically meaningful effects on study outcomes such as endurance and quality of life. In addition, longer follow-up of patients is critical to assess the durability of exercise behavior and any lasting effects of the exercise intervention.[5] Quantification of exercise among the control group patients is important to appropriately characterize the magnitude of effect of the intervention. Documentation of medication use during the post-HSCT period is also crucial; steroid use in particular can have profound effects on muscle mass and thus potentially on measures of strength and endurance. In the Baumann *et al*.[6] study, for example, seven patients in the training group vs one in the control group experienced grade III or IV acute GVHD, and corticosteroid use was therefore likely much greater in the training group, which actually could have diluted the impact of the exercise training in this study.

The Baumann *et al*.[6] study, taken together with others published before it, should provide the stimulus for a much larger, well-designed, multi-center trial that is powered to determine more conclusively whether exercise programs performed by HSCT recipients in the early period after transplantation can improve physical functioning and quality of life. The exercise program should be simple enough that patients can adopt it with minimal training and perform it with a reasonable degree of supervision and reinforcement; it should also be reproducible such that, if successful, it can be easily adopted in a variety of healthcare settings. Finally, researchers should evaluate whether the benefits of a well-executed exercise program are short-lived or are actually durable beyond the early post transplant period.

Until these additional RCT data are available, it seems reasonable based on consistent evidence of the safety and modest benefits of exercise from existing studies in both HSCT and non-transplant settings, for transplant centers to institute simple, structured, and low-impact exercise programs into clinical practice. Centers with exercise programs should incorporate appropriate screening for cardiovascular disease into the pre-HSCT evaluation. The available evidence from exercise research in HSCT, while generally less than desired on a methodological level, do support a move beyond current guidance that HSCT patients 'stay active' during their hospitalization.

Acknowledgements

We are grateful to Drs Andrew Artz, Karen Hagerty, and Jerome Seidenfeld for their thoughtful reviews of earlier grafts. The opinions expressed in this article are those of the authors and do not necessarily represent the views of the American Society of Clinical Oncology.

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