Biol Blood Marrow Transplant 25 (2019) e191–e198

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Report

Role of Physical Therapy before and after Hematopoietic Stem Cell Transplantation: White Paper Report

Jaleel Mohammed[1,2,*], Sean R. Smith[2,3], Linda Burns[4], Grzegorz Basak[5,15], Mahmoud Aljurf[2,6], Bipin N. Savani[2,7], Helene Schoemans[2,8], Zinaida Peric[2,9], Naeem A. Chaudhri[6], Nnenna Chigbo[2,10], Arun Alfred[2,11], Hadeel Bakhsh[2,12], Nina Salooja[13], Amah Chris Chim[14], Shahrukh K. Hashmi[2,6,16]

[1] *Department of Physical Therapy and Rehabilitation, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia*
[2] *Physical Therapy Association for Graft Versus Host Disease, Swindon, United Kingdom*
[3] *Department of Physical Medicine and Rehabilitation, University of Michigan, Ann Arbor, Michigan*
[4] *National Marrow Donor Program/Be The Match, Center for International Blood and Marrow Transplant Research, Minneapolis, Minnesota*
[5] *Medical University of Warsaw, Warsaw, Poland*
[6] *Oncology Centre, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia*
[7] *Department of Medicine, Vanderbilt University, Nashville, Tennessee*
[8] *University Hospitals of Leuven, Leuven, Belgium*
[9] *University Hospital Centre, Zagreb, Croatia*
[10] *Exercise Immunology/Palliative Care Unit, Department of Physiotherapy, University of Nigeria, Teaching Hospital, Enugu, Nigeria*
[11] *The Rotherham NHS Foundation Trust, South Yorkshire, United Kingdom*
[12] *Princes Nourah Bint Abdulrahman University, Riyadh, Saudi Arabia*
[13] *Department of Haematology, Hammersmith hospital, Imperial College, London, United Kingdom*
[14] *Paediatric Surgery Division, Department of Surgery, College of Medicine, University of Nigeria, Nsukka, Nigeria*
[15] *Transplant Complications Working Party, European Society for Blood and Marrow Transplantation, Barcelona, Spain*
[16] *Department of Medicine, Mayo Clinic, Rochester, Minnesota*

Article history:
Received 9 January 2019
Accepted 9 January 2019

Key Words:
Exercise
HSCT
Allogeneic
Physical therapy

A B S T R A C T

Hematopoietic stem cell transplantation (HSCT) patients can suffer from various musculoskeletal problems resulting in long-term functional incapacity. Physical therapy (PT), as a part of the healthcare team, has been historically advocated for regaining functional capacity and improving quality of life post-HSCT. Because of the nature of this condition and the burden of post-transplant complications, this patient group requires a unique approach toward their rehabilitation that takes into account their complex musculoskeletal presentation ranging from fascia, muscle, tendons, bones, and ligaments. However, to our knowledge there is no universal standardized PT protocol or pathway to help guide rehab specialists to achieve optimal gains for this patient group, and anecdotal evidence suggests that these patients do not always receive the PT care they require. Hence, in collaboration with the Transplant Complications Working Party of the European Society for Blood and Marrow Transplantation, the Survivorship Special Interest Group of the American Society of Blood and Marrow Transplantation, and the Quality of Life Committee of the Eastern Mediterranean Blood and Marrow Transplantation, herein the Physical Therapy Association for Graft Versus Host Disease provides a brief review on role of PT in mitigating musculoskeletal complications in HSCT patients and makes evidence-based recommendations for incorporation of PT into routine HSCT care.

INTRODUCTION

Quality of life (QoL) after hematopoietic stem cell transplantation (HSCT) is an area of growing importance because of the increase in number and survival of patients undergoing HSCT. Although advances in peritransplant care have improved survival [1], QoL post-HSCT can be compromised by myriad factors [2], including poor physical function, pre- and post-HSCT depression and distress, pretransplant oncologic treatments, development of acute and/or chronic graft-versus-host disease (GVHD) [4], lack of psychosocial support, medication adverse effects, pretransplant disease [3,4], and poor nutrition [5].

Rehabilitation is a broad term and refers to any type of comprehensive treatment program including physical, psychological, or social aspects. The role of physical therapy (PT) within the scope of rehabilitation in HSCT survivorship is wide ranging

Financial disclosure: See Acknowledgments on page e197.

* Correspondence and reprint requests: Jaleel Mohammed, PT, Physical Therapy Association for Graft Versus Host Disease, 12 Boscombe Down, Quedgely, Gloucester GL2 2FT, UK.
E-mail address: qualityfrlife@gmail.com (J. Mohammed).

https://doi.org/10.1016/j.bbmt.2019.01.018
1083-8791/

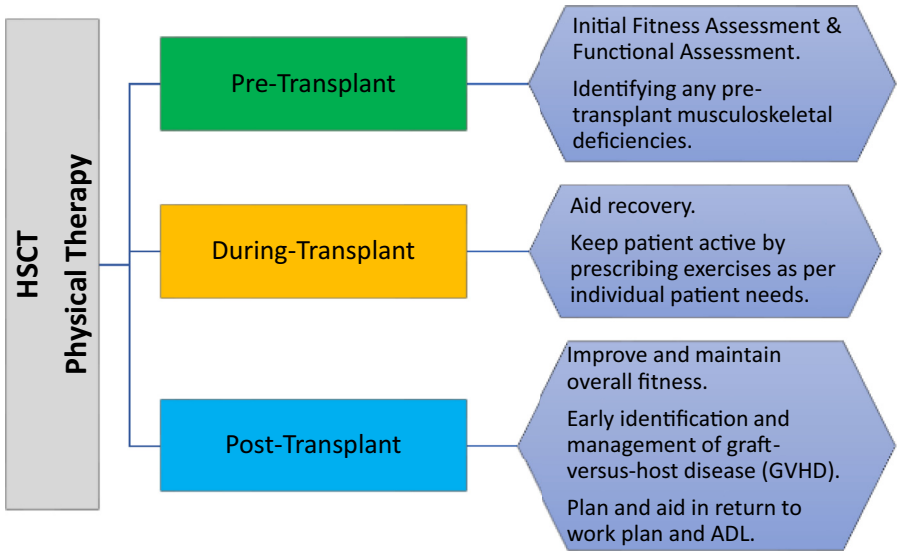

Figure 1. Role of PT in HSCT.

but not well defined, so providers and patients may not be aware of the benefits that PT can offer both pre and post-HSCT to the patients. Furthermore, skilled rehabilitation providers familiar with this complex patient population at a given institution may be lacking, creating another barrier to care.

This white paper reviews the benefits of physical rehabilitation in patients undergoing HSCT and provides recommendations for incorporating PT into standard HSCT survivorship care. The Physical Therapy Association for Graft Versus Host Disease is an organization of experts comprised of physical therapists, occupational therapists (OTs), and transplant clinicians working together to streamline the efforts of physical therapists and OTs needed for all physical domains of HSCT patients' physical functioning and QoL. In collaboration with the Transplant Complications Working Party of the European Society for Blood and Marrow Transplantation, the Survivorship Special Interest Group of the American Society of Blood and Marrow Transplantation, and the Quality of Life Committee of the Eastern Mediterranean Blood and Marrow Transplantation, herein the Physical Therapy Association for Graft Versus Host Disease provides a brief review on role of PT in mitigating musculoskeletal (MSK) complications in HSCT patients and makes evidence-based recommendations for incorporation of PT into routine HSCT care.

ROLE OF PT IN HSCT

The evaluation of physical rehabilitation after HSCT dates to at least 1986 [6], and over time several studies have shown that patients engaging in meaningful exercise programs require less physical support for activities of daily living and less reliance on their caregivers for large portions of the day [7]. However, healthcare professionals are increasingly aware that patients awaiting HSCT can present with various complex medical problems that have a direct impact on their functional capacity [8]. Hence, involving PT before transplant should be an essential part of the pretransplant assessment process, where the patient receives a full body physical examination, which includes objective measurements of strength and endurance, that can act as a baseline score for monitoring improvement or deterioration. Because HSCT survivors are a unique population (due to the effects of chemotherapy and/or GVHD on MSK systems), the traditional role of PT in identifying and addressing disability may not be enough for an optimum physical and occupational health assessment; thus, an enhanced role of rehabilitation specialists working together with clinicians is required to prevent disability and to ensure long-term maintenance of physical function (Figure 1).

PT CONSULTATION PRETRANSPLANT

Literature is lacking on the exact role of PT services pre-HSCT and its impact on long-term outcomes. Despite the lack of data, it makes intuitive sense to consider assessments of physical functioning pre-HSCT to have a baseline for comparison post-HSCT; however, evidence for the efficacy of such an approach is urgently needed. Many cancer patients pre-HSCT undergo some sort of chemotherapy (including corticosteroids) that can affect physical functioning. Thus, certain assessments pre-HSCT, as outlined in Table 1, can help in the following ways:

1. Pretransplant fitness level can have a positive influence on recovery and QoL [9]. The physical therapist can evaluate pretransplant fitness levels and design an exercise program to possibly help influence recovery.

Table 1
Pretransplant Functional Evaluation of the MSK System

Subjective Measures	Objective Measures	Aims	Means	Outcomes
VAS score: 5/10 for pain in the left shoulder and arm DASH questionnaire score = 60/100	Bilateral shoulder range of motion: abduction only 120 degrees, JAMAR dynamometer grip strength bilateral = 10 kg	Reduce pain, improve range of motion of shoulder, improve strength in hand	Myofascial work, TENS, joint mobilization, home exercises, progressive resistance training	Pain reduced to 3/10, shoulder range of motion improved to 150 degrees, grip strength improved to 12 kg

VAS indicates visual analog scale; DASH, disabilities of the arm, should, and hand; JAMAR, hydraulic hand dynamometer; TENS, transcutaneous electrical nerve stimulations.

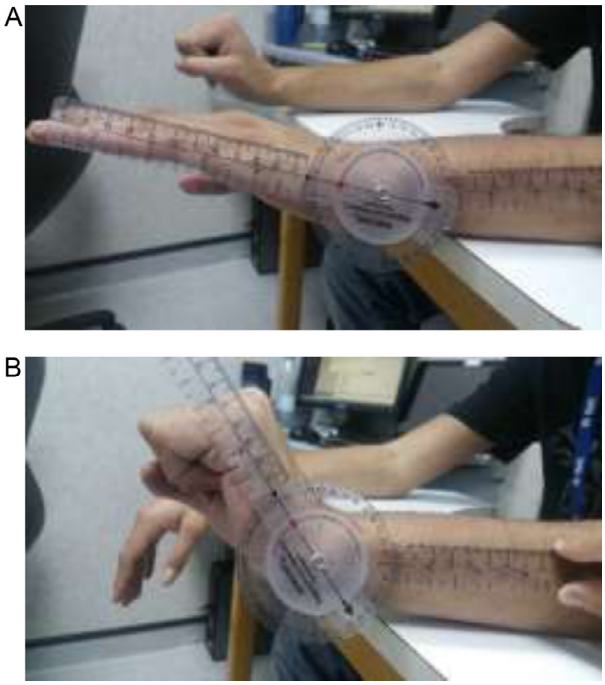

Figure 2. Wrist maneuvers in PT assessment. (A) Wrist extension 13 degrees when fingers are open. (B) Wrist extension 52 degrees when fingers are closed.

2. A full body functional evaluation before transplant may help in early identification of any functional loss [10].
3. Baseline functional scores can act as an important tool when carrying out PT interval assessments, not only while the patient is admitted in hospital but also post-transplant while planning an exercise program aimed at returning to the pretransplant level of activities of daily life or when making return to work recommendations [11].
4. A pretransplant full body functional evaluation has also shown to be helpful in identifying high-risk patients with existing MSK functional deficiencies, thereby highlighting the need for more focused rehabilitation needs during and after the transplant [10] (Figure 2).
5. Physical activity throughout the continuum of the transplant course has been shown to be beneficial in improving physical function and reducing fatigue [12].

A general overview on the benefits of PT on various health parameters has been outlined in the Table 2.

PT IN HSCT SURVIVORSHIP

Some form of exercise or PT is routinely prescribed by physical therapists for patients before, during, and after HSCT aimed at improving QoL, reducing disease burden, improving physical function, assisting reintegration to social activities, and returning to work and normal activities of daily life. Cancer patients, in general, can experience deterioration in their physical work ability that can last from 2 to 6 years after diagnosis [11], and this may be more pronounced in patients after HSCT

Table 2
Outcome from the PT Intervention

Authors and Year of Study	Main Parameter	Outcome
Kim (2003)	Fatigue	Relaxation breathing exercise can improve fatigue.
Mello, Tanaka, and Dulley (2003)	Muscle strength	Exercises are efficient in promoting an increase in muscle strength.
Kim and Kim (2005)	Anxiety and depression	Relaxation breathing exercise can improve anxiety and depression levels.
Coleman et al. (2008)	Hemoglobin	Exercise can help decrease the need for transfusions.
Jarden et al. (2009)	Diarrhea, QoL, fatigue, and psychological wellbeing	Exercise can help decrease intensity of diarrhea and days receiving total parenteral nutrition while undergoing allo-HSCT and improve QoL, fatigue, and psychological well-being up to 6 months after allo-HSCT.
Shelton et al. (2009)	Functional capacity	Short-term exercise training regardless of how the training program is supervised can help improve patient functional capacity.
Chamorro-vin et al. (2010)	Immune cell recovery and body mass index	Moderate-intensity exercise training does not negatively affect immune cell recovery in children with high-risk cancer while contributing to increasing body mass and body mass index.
Baumann et al. (2011)	Physiologic, psychological, and psychosocial	Physical exercise was found to be feasible and safe with a positive impact on patient's physiologic, psychological, and psychosocial constitution.
Knols et al. (2011)	Health-related QoL and fatigue	Physical exercise has a positive impact on health-related QoL and fatigue.
Tran et al. (2012)	Respiratory	Pulmonary rehabilitation appears to improve 6-minute walk distance, subjective symptoms of dyspnea, and exercise tolerance in patients with bronchiolitis obliterans syndrome.
Morishita et al. (2013)	Cytopenia, QoL, and physiologic function	PT was found to be safe and beneficial in cytopenic patients and can help improve physiologic function and QoL.
Jacobsen et al. (2014)	Muscle mass	Exercise therapy can help to maintain lower extremity muscle mass.
Takekiyo et al. (2015)	Muscle strength, fatigue, and functional capacity	Strength training intervention can enhance early recovery after HCT and reduce fatigue while maintaining and/or improving muscle strength and functional ability.
Hacker et al. (2016)	QoL and fatigue	Structured physical activity programs have positive effects on QoL and fatigue scores.
Kabak et al. (2016)	Cardiorespiratory fitness	Home-based, personalized intensive exercise programs have the potential to improve cardiorespiratory fitness.
Wood et al. (2016)	Fatigue, physical performance, and functional capacity	Physical exercise is beneficial for patients before, during, and after allo-HSCT and can significantly alter cancer-related fatigue in the context of allo-HSCT and improve physical performance and functioning.
Schumacher et al. (2018)	Endurance strength QoL	Exercise had a favorable effect on physical fitness, fatigue, and QoL and exergaming is capable of eliciting physical activity intensity similar to that of moderate exercise.

who have a low return-to-work rate [12]. However, caution must be exercised in extrapolating data from studies in cancer patients because HSCT patients are a unique population. A detailed description regarding evidence on the role physical therapists and OTs in each functional or QoL aspect in HSCT patients is beyond the scope of this white paper report, and readers are advised to refer to other peer-reviewed publications (eg, James MC, et al. Physical therapy for patients after bone marrow transplantation. Physical Ther. 1987;67:946-952; Mohammed et al. Is there any role for PT in chronic GvHD? Bone Marrow Transplant. 2018;53:22; Steinberg A, et al. The role of physical rehabilitation in stem cell transplantation patients. Support Care Cancer. 2015;23:2447-2460).

There are several reported benefits of physical activity and early mobilization in the HSCT population. First, resistance and aerobic exercises have been shown to have a positive influence on exercise capacity, minimized loss of functional performance, decreased intensity of diarrhea, and decreased days receiving total parenteral nutrition after allogeneic HSCT [13]. Second, self-directed, home-based interval exercise training improves cardiovascular fitness in HSCT patients [14] and can reduce fatigue and distress [15]. Third, structured but individualized exercise programs throughout the continuum of HSCT increases functional performance, muscle strength, and mobility [16]. Fourth, exercise during pediatric HSCT is not only feasible, but it also contributes to prevention of treatment-related loss of physical function [13]. Finally, use of mixed-exercise, progressive relaxation, and psychoeducation have been shown to improve strength and endurance in allo-HSCT patients [17].

In general, we agree with (and would reinforce) the guidelines published by the American Society of Blood and Marrow Transplantation American, European Society for Blood and Marrow Transplantation, Asia Pacific Blood and Marrow Transplantation (APBMT), Bone Marrow Transplant Society of Australia and New Zealand (BMTSANZ), Eastern Mediterranean Blood and Marrow Transplantation, and Brazilian Society for Bone Marrow Transplantation (SBTMO) that indicate transplant recipients should follow the general population age-specific guidelines for physical activity.

IMPAIRMENT-DRIVEN REHABILITATION POST-HSCT

Some of the common problems faced by patients post-HSCT are impaired cardiopulmonary capacity, steroid myopathy, chronic fatigue, deconditioning, multifactorial sarcopenia, and chronic GVHD [18]. Furthermore, chronic GVHD can affect many organ systems [19–25], and as a result patients may develop impairments ranging from imbalance, weakness, loss of range of motion, and pain. PT, when directed to target specific impairments in HSCT patients, can have profound benefits beyond that of broadly prescribing "exercise." Rather, rehabilitation interventions should be targeted to each impairment. Below are some relatively common problems experienced by patients post-HSCT and the role of physical rehabilitation.

Fatigue

One of the major challenges experienced by the HSCT survivor is severe fatigue, which can occur in 3% to 41% of long-term transplant survivors lasting from 1 to 15 years [26]. The etiology is unknown and may be multifactorial, including reduced physical activity and adverse side effects of necessary post-transplant medication [27]. Physical activity has shown to be effective in minimizing post-HSCT fatigue [28], even more than pharmacologic management with neurostimulant medications. Physical therapists and other rehabilitation providers (eg, OTs, speech therapists) experienced in working with HSCT patients are generally knowledgeable about the adverse effects of commonly used drugs in this context, and this places them in a unique position in monitoring for related MSK symptomatology of patients and reporting concerns to the medical teams for timely action.

Steroid Myopathy

Steroid myopathy is a relatively common complication in patients who develop acute or chronic GVHD for which corticosteroid therapy is often the first line of immunosuppression. There is a dose-related effect, and as little as a daily dose of 10 mg of prednisone can cause proximal bilateral lower extremity weakness [29]. This typically affects type 2 muscle fibers, which are used for short bursts of strength, such as in climbing stairs or getting up from a low seat (eg, a toilet seat) [30]. As a result, patients are at risk of falls and eventually losing independence. A strong correlation has been reported with corticosteroid dose and the reduction in muscle strength, for example, with knee extensor muscles, hand grip [31], and respiratory muscles [32]. An individualized exercise prescription based on the patient's baseline medical, physical, and functional evaluation has been shown to have a positive impact on steroid-induced myopathy [33], and rehabilitation interventions can provide patients with adaptive techniques and equipment to overcome barriers while they are regaining muscle strength.

Chronic GVHD with Fascial Involvement

Chronic GVHD can result in joint destruction and associated pain and loss of range of motion [20,34,35]. Chronic GVHD can affect multiple joints, but hands and fingers are usually affected first, resulting in reduced function and range of motion [36] (Figure 2).

Because of the complex nature of fascial involvement, one should bear in mind that the standard range of motion assessment can fail to capture the complete picture [17], and hence an experienced physical therapist with knowledge of fascial patterns can help identify and intervene at early stages of the disease process. Figure 2A,B demonstrates the significant variance in wrist extension range of motion recordings, when fingers are open compared with when fingers are closed. PT that includes a combination of stretching and splinting has been shown to improve range of motion in patients with sclerotic (fascial) chronic GVHD [37]. However, standard splinting for the hands and forearms may not be suitable for these patients, so therapists experienced in splinting and the knowledge of the fascial patterns modify the splint to the needs of the patient. Figure 3 shows an example of a standard splint, which fails to address the finger flexion problem in this patient. Other modalities that may improve range of motion include immersing

Figure 3. Dynamic splinting for patients having finger GVHD resulting in flexion problems.

the affected joint in hot melted paraffin wax baths, but these modalities have not been studied in the GVHD population.

Avascular Necrosis

Patients on chronic glucocorticoid therapy are at risk of developing avascular necrosis of their joints, leading to pain and range of motion reduction. Although joint replacement is ultimately the cure for this problem, it is not always a viable option because of patient health status or the joint with avascular necrosis may not be amenable to replacement. Therefore, PT can play an important role in strengthening the muscles surrounding the affected joint to help reduce pain. Adaptive equipment may also be prescribed to patients to offload the joint, allowing improved mobility and improving the QoL. Additionally, some data suggest that extracorporeal shock wave therapy may reduce avascular necrosis–
associated hip pain post-HSCT [38], with significant benefits on QoL, pain, and functional performance in patients with Association Research Circulation Osseous Stage Grade I and II avascular necrosis [39].

In addition to exercises and electrotherapy, manual therapy can also play a major role in patients suffering from various joint and fascial problems. Myofascial release technique is used by physical therapists to help release tensed or restricted fascia in select patient groups [40].

Cardiopulmonary Impairments Post-HSCT

Many post-HSCT patients have impaired aerobic capacity and decreased physical activity compared with cohorts without HSCT [41]. Physical activity and exercise can prevent the decline in function and restore exercise capacity in patients after transplant [42,43].

Additionally, patients may develop pulmonary chronic GVHD, which is associated with bronchiolitis obliterans syndrome, characterized by symptoms of dyspnea, cough, and wheezing. Although treatment options remain limited for this condition, pulmonary rehabilitation has shown to have a positive impact on QoL and general overall function in patients by improving breathing capacity and subjective dyspnea [44].

Osteopenia and Osteoporosis

Although exercise has been shown to improve bone mass density, the type of exercises prescribed is vital in achieving the desired results. Widely practiced exercises like cycling, walking, and swimming usually do not produce any meaningful bone stimulating effect [45]. Bone health can mainly be influenced by performing well-designed, high-impact, weight-bearing activities such as progressive resistance training, jumping, hopping, and combination exercises [46]. It is equally important to maintain an optimum intake of calcium and vitamin D and to treat hypothyroidism or hyperthyroidism if present. Deficiencies of thyroid hormones or vitamin D/calcium can significantly hinder the success of a structured exercise program for osteopenia and osteoporosis.

Effects on Sexual Health

HSCT can impact physical sexual function in a variety of ways, including GVHD affecting the genitals and pelvic floor muscle weakness from sarcopenia and/or steroid use [47]. Physical therapists trained in pelvic floor rehabilitation can play a significant role in improving patient sexual health by educating and instructing patients on exercises aimed at improving pelvic floor strength and reducing symptom burden [48]. However, data specifically on the outcomes of pelvic floor exercises in HSCT patients are lacking.

PT AND THE SAFETY OF PHYSICAL ACTIVITY AFTER HSCT

Patients post-HSCT invariably have cytopenias increasing the risk of bleeding and infection, so physical activity should be monitored by a skilled therapist in this setting. A physical therapist experienced in working with HSCT patient groups will constantly monitor their patients and make necessary modifications to the exercise prescription to reflect the patients' daily needs and safety. Thrombocytopenia is sometimes considered as a contraindication to exercises [49]; however, a therapist-guided exercise program has shown to be safe, effective, and feasible in HSCT patients even with thrombocytopenia [50]. Normally, a platelet count less than 20,000/mL would be considered as a relative contraindication for exercises, whereas patients with platelet counts between 20,000 and 30,000/mL could perform gentle nonresistance exercises, 30,000 to 50,000/mL minimal resistance (1 to 2 pound) exercises, 50,000 to 150,000/mL progressive resisted exercises, and 150,000/mL and beyond no restrictions [51]. There is, however, growing evidence that even with critically low platelets (10,000 to 50,000 /mL), patients can perform carefully designed exercises without any additional risk factors, if they are monitored and supervised by an experienced therapist [52,53].

OUTCOME MEASURES

Physical therapists are trained in appropriate goal setting and working with specific, measurable, achievable, relevant and time-bound, or SMART, goals that help the therapist and the patient evaluate the treatment against the outcome [54]. Table 3 outlines some of the subjective and objective measures that can be generally useful when assessing patients.

RETURN TO WORK POST-HSCT

Work life is not only an important component of QoL for many patients, but returning to work for many individuals is

Table 3
Subjective and Objective Assessment Measures

Subjective Assessment	Objective Assessment
QoL: PROMIS, EQ-5D, SF-36, FACT-BMT	Range of motion: goniometry, photographic range of motion, inclinometers
Functional: Patient-Specific Functional Scale, DASH- Upper Limb, Lower Limb Functional Scale, Foot and Ankle Disability Index, Patient Rate wrist/hand Evaluation, Neck Disability Index	Cardiorespiratory: VO_{2Max} - single-stage 6-minute submaximal exercise test, the Astrand and Rhyming cycle ergometer test, 2-minute stair climb test, Shuttle run test, wrist actigraphy, spirometry for lung capacity, 6-minute walk test, time up-and-go test
Pain: Brief Pain Inventory-Short Form, VAS, McGill Pain Questionnaire, P4 Pain Questionnaire	Muscle strength: timed stair climb, hand grip strength, 30-second chair-stand test, time needed to stand up from bedrest exam, leg-lift test, repeated squat test, sit-up test, sit-and-reach test, back extension test, isotonic muscular strength, maximal isometric voluntary strength
Yellow and Blue Flags: FABQ, Orebro Questionnaire, TAMPA Scale of Kinesiophobia	

PROMIS indicates Patient-Reported Outcomes Measurement Information System; EQ-5D, SF-36, FACT-BMT, Functional Assessment of Cancer Therapy-Bone Marrow Transplant; FABQ, Fear Avoidance Belief Questionnaire; Orebro, The Örebro Musculoskeletal Pain Questionnaire; TAMPS, Tampa Scale for Kinesiophobia.

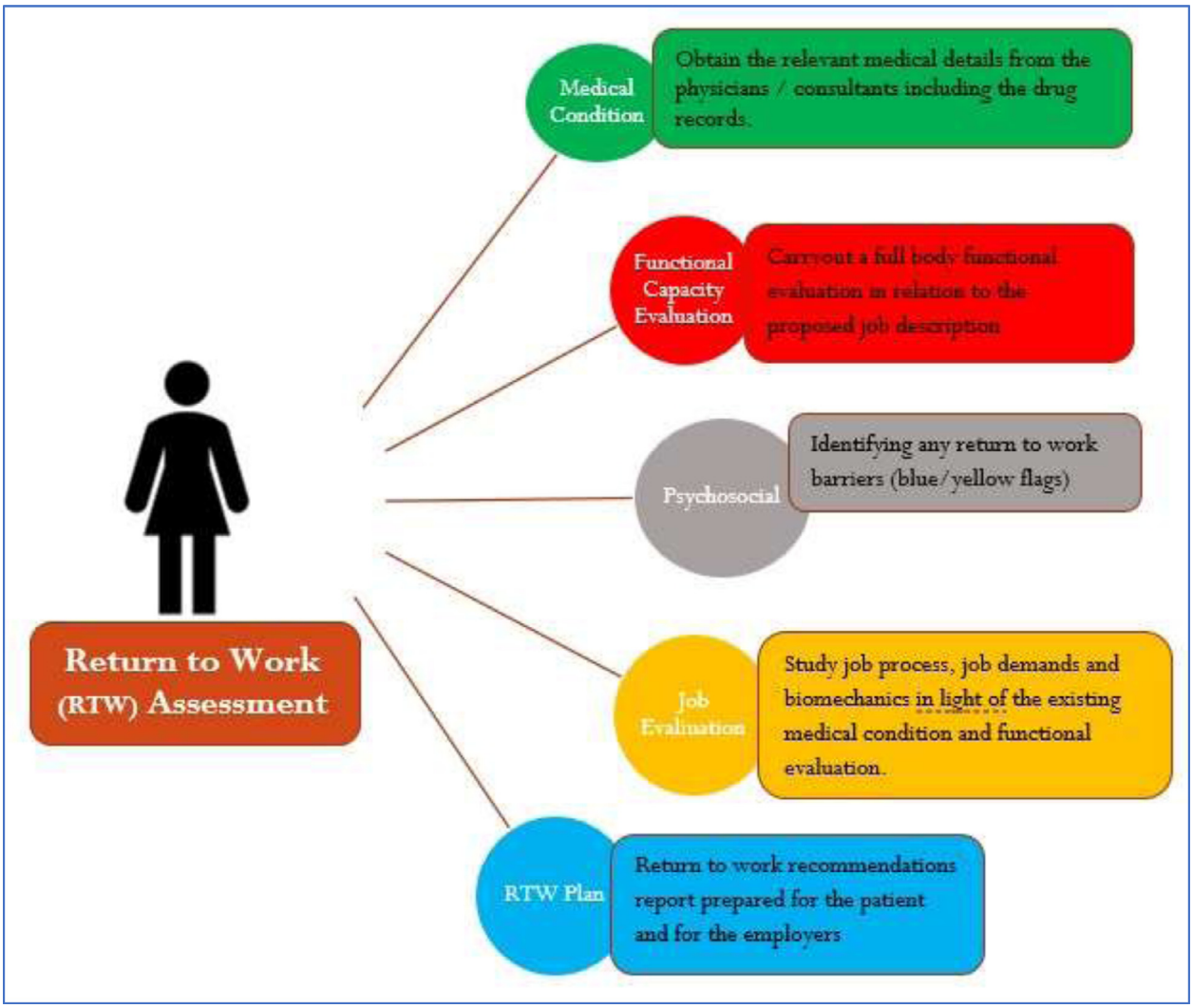

Figure 4. Return to work process.

an indicator of complete recovery (Figure 4). Cancer patients can experience a deterioration in physical work ability that can last from 2 to 6 years after diagnosis [55]. Physical therapists trained in occupational health are optimally placed to carry out pre-employment physical and functional testing, thereby helping both employees and employers make informed decisions on job suitability [56].

The physical therapist, with the patient's permission, can potentially liaise with employers and advise on the type and kind of work one can undertake including a phased return to work. Phased return to work can include workplace adjustments, modified or reduced working hours, modified work tasks, stepwise escalation of work, modified workplaces, and regular communication with or between managers, colleagues, and health professionals.

Disability in cancer can be episodic, and hence patients require ongoing support from both medical and rehabilitation teams [57]. We recommend that wherever possible occupational health specialist(s) and physical therapist(s) (experienced in return to work functional capacity evaluation) assess patients both in the inpatient and outpatient setting as part of a multidisciplinary team that designs a return to work–specific rehabilitation program and monitors progression toward that goal. Return to work functional assessment has many aspects to it, and Figure 2 illustrates the main features of a return to work functional assessment process.

Finally, some patients' return to work plan can be affected by factors other than impaired physical function. Some studies have reported that more than 50% of HSCT patients suffer from cognitive problems involving memory, attention and concentration, decision-making, visual memory, and motor function [58,59]. Any return to work assessment should take into consideration the cognitive aspect of the problem in this patient group so that appropriate support can be extended to patients willing to return to work. Some studies have demonstrated a positive impact of structured exercises on cognitive function [60,61], and thus exercises can be a used as an adjunct to other therapies in managing cognitive problems. Return to work recommendations include that physical therapists and/or OTs assess the goals of functional recovery suitable for the workplace, establish a liaison with both clinicians and employers, evaluate the type and extent of disability, and evaluate the functional assessment of structured exercises for cognitive function.

FUTURE DIRECTIONS

The paucity of evidence in the field of PT makes it difficult to make firm recommendations; however, a summary of

general guidance is presented to help both physical therapists and clinicians caring for HSCT patients in optimizing collaborative care. Lack of evidence underscores the urgent unmet need for clinical trials in this arena. Additionally, the basis of MSK pathology in HSCT patients and the biologic basis of physical therapist and/or OT interventions needs to be established via translational research in the current era of transcriptomics, metabolomics, and proteomics.

ACKNOWLEDGMENTS

The authors acknowledge the critical review of the manuscript and constructive feedback from the Steering Committee of the American Society of Blood and Marrow Transplant's Survivorship Special Interest Group, the Late Effects Subcommittee of the Transplant Complications Working Party of the European Society for Blood and Marrow Transplantation, and the Late Effects, Supportive Care, and Quality of Life Committee of the Eastern Mediterranean Blood and Marrow Transplantation Group.

Financial disclosure: The authors have nothing to disclose.

Conflict of interest statement: S.K.H. has received honorarium from Mallinckrodt.

Authorship statement: J.M., S.R.S., and S.K.H. wrote the first draft of the manuscript. All authors contributed substantially to the conception, acquisition, analysis, and interpretation of the data for the work.

REFERENCES

1. Copelan EA. Hematopoietic stem-cell transplantation. *N Engl J Med*. 2006;354:1813–1826.
2. Mosher CE, DuHamel KN, Rini C, Corner G, Lam J, Redd WH. Quality of life concerns and depression among hematopoietic stem cell transplant survivors. *Support Care Cancer*. 2011;19:1357–1365.
3. Weis J, Tomaszewski KA, Hammerlid E, et al. International psychometric validation of an EORTC quality of life module measuring cancer related fatigue (EORTC QLQ-FA12). *J Natl Cancer Inst*. 2017;109(5).
4. Pallua S, Giesinger J, Oberguggenberger A, et al. Impact of GvHD on quality of life in long-term survivors of haematopoietic transplantation. *Bone Marrow Transplant*. 2010;45:1534–1539.
5. Lipkin AC, Lenssen P, Dickson BJ. Nutrition issues in hematopoietic stem cell transplantation: state of the art. *Nutr Clin Pract*. 2005;20:423–439.
6. Cunningham BA, Morris G, Cheney CL, Buergel N, Aker SN, Lenssen P. Effects of resistive exercise on skeletal muscle in marrow transplant recipients receiving total parenteral nutrition. *J Parent Enteral Nutr*. 1986; 10:558–563.
7. Atkinson T, Lassiter M. Low Impact Physical Functioning-BMT Bootcamp Program. *Biol Blood Marrow Transplant*. 2017;23:S469.
8. 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.
9. Wallek S, Senn–Malashonak A, Vogt L, Schmidt K, Bader P, Banzer W. Impact of the initial fitness level on the effects of a structured exercise therapy during pediatric stem cell transplantation. *Pediatr Blood Cancer*. 2018;65(2).
10. Mohammed J, AlGhamdi A, Hashmi SK. Full-body physical therapy evaluation for pre-and post-hematopoietic cell transplant patients and the need for a modified rehabilitation musculoskeletal specific grading system for chronic graft-versus-host disease. *Bone Marrow Transplant*. 2018;53(5).
11. De Boer AG, Taskila T, Ojajärvi A, Van Dijk FJ, Verbeek JH. Cancer survivors and unemployment: a meta-analysis and meta-regression. *JAMA*. 2009;301:753–762.
12. Morrison EJ, Ehlers SL, Bronars CA, et al. Employment status as an indicator of recovery and function one year after hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant*. 2016;22:1690–1695.
13. 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.
14. Wood WA, Phillips B, Smith-Ryan AE, et al. Personalized home-based interval exercise training may improve cardiorespiratory fitness in cancer patients preparing to undergo hematopoietic cell transplantation. *Bone Marrow Transplant*. 2016;51:967–972.
15. Wiskemann J, Dreger P, Schwerdtfeger R, et al. Effects of a partly self-administered exercise program before, during, and after allogeneic stem cell transplantation. *Blood*. 2011;117:2604–2613.
16. Yildiz Kabak V, Duger T, Uckan Cetinkaya D. Investigation of the effects of an exercise program on physical functions and activities of daily life in pediatric hematopoietic stem cell transplantation. *Pediatr Blood Cancer*. 2016;63:1643–1648.
17. Jarden M, Hovgaard D, Boesen E, Quist M, Adamsen L. Pilot study of a multimodal intervention: mixed-type exercise and psychoeducation in patients undergoing allogeneic stem cell transplantation. *Bone Marrow Transplant*. 2007;40:793–800.
18. Steinberg A, Asher A, Bailey C, Fu JB. The role of physical rehabilitation in stem cell transplantation patients. *Support Care Cancer*. 2015;23:2447–2460.
19. Lee SJ, Vogelsang G, Flowers ME. Chronic graft-versus-host disease. *Biol Blood Marrow Transplant*. 2003;9:215–233.
20. Flowers MED, Vogelsang GB. Clinical manifestations and natural history. In: Vogelsang GB, Pavletic SZ, eds. *Chronic Graft Versus Host Disease: Interdisciplinary Management*. New York, NY: Cambridge University Press; 2009:56–69.
21. Haruki H, Koga M, Ogasawara JI, Omoto M, Kawai M, Kanda T. Neuropathy in chronic graft–versus–host disease caused by Donor T cells. *Muscle Nerve*. 2012;46:610–611.
22. Martires KJ, Baird K, Steinberg SM, et al. Sclerotic-type chronic GVHD of the skin: clinical risk factors, laboratory markers, and burden of disease. *Blood*. 2011;118:4250–4257.
23. Markusse HM, Dijkmans BA, Fibbe WE. Eosinophilic fasciitis after allogeneic bone Marrow Transplant. *J Rheumatol*. 1990;17:692–694.
24. Spiryda LB, Laufer MR, Soiffer RJ, Antin JA. Graft-versus-host disease of the vulva and/or vagina: diagnosis and treatment. *Biol Blood Marrow Transplant*. 2003;9:760–765.
25. Nylander E, Wahlin YB, Lundskog B, Wahlin A. Genital graft-versus-host disease in a male following allogeneic stem cell transplantation. *Acta Dermatovenereol*. 2007;87:367–368.
26. Gielissen MF, Schattenberg AV, Verhagen CA, Rinkes MJ, Bremmers ME, Bleijenberg G. Experience of severe fatigue in long-term survivors of stem cell transplantation. *Bone Marrow Transplant*. 2007;39:595–603.
27. Kumar A, Mhaskar AR, Reljic T, et al. Antithymocyte globulin for acute-graft-versus-host-disease prophylaxis in patients undergoing allogeneic hematopoietic cell transplantation: a systematic review. *Leukemia*. 2012;26:582–588.
28. 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.
29. Lee HJ, Oran B, Saliba RM, et al. Steroid myopathy in patients with acute graft-versus-host disease treated with high-dose steroid therapy. *Bone Marrow Transplant*. 2006;38:299–303.
30. Pereira RMR, Carvalho JFD. Glucocorticoid-induced myopathy. *Joint Bone Spine*. 2011;78:41–44.
31. Morishita S, Kaida K, Yamauchi S, et al. Relationship between corticosteroid dose and declines in physical function among allogeneic hematopoietic stem cell transplantation patients. *Support Care Cancer*. 2013;21:2161–2169.
32. Kovalszki A, Schumaker GL, Klein A, Terrin N, White AC. Reduced respiratory and skeletal muscle strength in survivors of sibling or unrelated donor hematopoietic stem cell transplantation. *Bone Marrow Transplant*. 2008;41:965–969.
33. LaPier TK. Glucocorticoid-induced muscle atrophy: the role of exercise in treatment and prevention. *J Cardiopulm Rehabil Prevent*. 1997;17:76–84.
34. Janin A, Socie G, Devergie A, et al. Fasciitis in chronic graft-versus-host disease: a clinicopathologic study of 14 cases. *Ann Intern Med*. 1994;120:993–998.
35. Rennie JA, Auchterlonie IA. Rheumatological manifestations of the leukaemias and graft versus host disease. *Baillière's Clin Rheumatol*. 1991;5:231–251.
36. Inamoto Y, Pidala J, Chai X, et al. Assessment of joint and fascia manifestations in chronic graft–versus–host disease. *Arthritis Rheumatol*. 2014;66:1044–1052.
37. Beredjiklian PK, Drummond DS, Dormans JP, Davidson RS, Brock GT, August C. Orthopaedic manifestations of chronic graft-versus-host disease. *J Pediatr Orthopaed*. 1998;18:572–575.
38. Sun W, Gao F, Guo W, et al . Focused extracorporeal shock wave for osteonecrosis of the femoral head with leukemia after allo-HSCT: a case series. *Bone Marrow Transplant*. 2016;51:1507.
39. Vulpiani MC, Vetrano M, Trischitta D, et al. Extracorporeal shock wave therapy in early osteonecrosis of the femoral head: prospective clinical study with long-term follow-up. *Arch Orthop Trauma Surg*. 2012;132:499–508.
40. Beardsley C, Škarabot J. Effects of self-myofascial release: a systematic review. *J Bodywork Move Ther*. 2015;19:747–758.
41. Smith SR, Haig AJ, Couriel DR. Musculoskeletal, neurologic, and cardiopulmonary aspects of physical rehabilitation in patients with chronic graft-versus-host disease. *Biol Blood Marrow Transplant*. 2015;21:799–808.
42. Kim SD, Kim HS. Effects of a relaxation breathing exercise on fatigue in haemopoietic stem cell transplantation patients. *J Clin Nurs*. 2005;14:51–55.
43. Baumann FT, Zopf EM, Nykamp E, et al. Physical activity for patients undergoing an allogeneic hematopoietic stem cell transplantation: benefits of a moderate exercise intervention. *Eur J Haematol*. 2011; 87:148–156.
44. Tran J, Norder EE, Diaz PT, et al . Pulmonary rehabilitation for bronchiolitis obliterans syndrome after hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant*. 2012;18:1250–1254.

45. Rector RS, Rogers R, Ruebel M, Hinton PS. Participation in road cycling vs running is associated with lower bone mineral density in men. *Metabolism*. 2008;57:226–232.
46. Beck BR, Daly RM, Singh MA, Taaffe DR. Exercise and Sports Science Australia (ESSA) position statement on exercise prescription for the prevention and management of osteoporosis. *J Sci Med Sport*. 2017;20:438–445.
47. Thygesen KH, Schjødt I, Jarden M. The impact of hematopoietic stem cell transplantation on sexuality: a systematic review of the literature. *Bone Marrow Transplant*. 2012;47:716–724.
48. Rosenbaum TY. Pelvic floor involvement in male and female sexual dysfunction and the role of pelvic floor rehabilitation in treatment: a literature review. *J Sex Med*. 2007;4:4–13.
49. Baumann FT, Kraut L, Schule 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.
50. Rexer P, Kanphade G, Murphy S. Feasibility of an exercise program for patients with thrombocytopenia undergoing hematopoietic stem cell transplant. *J Acute Care Phys Ther*. 2016;7:55–64.
51. James MC. Physical therapy for patients after bone Marrow Transplant. *Phys Ther*. 1987;67:946–952.
52. Elter T, Stipanov M, Heuser E, et al. Is physical exercise possible in patients with critical cytopenia undergoing intensive chemotherapy for acute leukaemia or aggressive lymphoma? *Int J Hematol*. 2009;90:199–204.
53. Ibanez K, Espiritu N, Souverain RL, et al. Safety and feasibility of rehabilitation interventions in children undergoing hematopoietic stem cell transplant with thrombocytopenia. *Arch Phys Med Rehabil*. 2017;99(2):226–233.
54. Bowman J, Mogensen L, Marsland E, Lannin N. The development, content validity and inter–rater reliability of the SMART–goal evaluation method: a standardised method for evaluating clinical goals. *Austral Occupat Ther J*. 2015;62:420–427.
55. De Boer AG, Taskila T, Ojajärvi A, Van Dijk FJ, Verbeek JH. Cancer survivors and unemployment: a meta-analysis and meta-regression. *JAMA*. 2009;301:753–762.
56. The Chartered Society of Physiotherapy. (2019). Download Physiotherapy Works for Fitness for Work. [online] Available at: http://www.csp.org.uk/publications/download-physiotherapy-works-fitness-work. [Accessed Jun 23, 2018].
57. de Boer AG, Taskila TK, Tamminga SJ, Feuerstein M, Frings–Dresen MH, Verbeek JH. Interventions to enhance return–to–work for cancer patients. *Cochrane Library*. 2015;(9).
58. Harder H, Cornelissen JJ, Van Gool AR, Duivenvoorden HJ, Eijkenboom WM, van den Bent MJ. Cognitive functioning and quality of life in long–term adult survivors of bone Marrow Transplant. *Cancer*. 2002;95:183–192.
59. Syrjala KL, Artherholt SB, Kurland BF, et al. Prospective neurocognitive function over 5 years after allogeneic hematopoietic cell transplantation for cancer survivors compared with matched controls at 5 years. *J Clin Oncol*. 2011;29:2397–2404.
60. Schmitz KH, Courneya KS, Matthews C, et al. American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. *Med Sci Sports Exerc*. 2010;42:1409–1426.
61. Tseng CN, Gau BS, Lou MF. The effectiveness of exercise on improving cognitive function in older people: a systematic review. *J Nurs Res*. 2011;19:119–131.