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The role of physical rehabilitation in stem cell transplantation patients

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Abstract

The purpose of this paper is to review the evidence for the role of physical rehabilitation in stem cell transplantation patients. We will also review the literature and discuss professional experiences on how rehabilitation can play a role in stem cell transplant care and survivorship. Hematopoietic stem cell transplantation (HCT) is a procedure that has evolved substantially over the years to help treat multiple conditions, particularly hematologic malignancies. HCT can be very stressful on the body and can leave patients weakened and sometimes quite debilitated. Supportive care measures have advanced to improve the quality of life and overall survival of HCT survivors. One key component of improved supportive care is gaining increased attention, and that is physical medicine and rehabilitation. Its role in HCT survivorship care is expanding, and new insight and research within the discipline have focused on fatigue, inflammation, exercise, and the development of structured rehabilitation programs to improve the musculoskeletal sequelae of transplantation. This literature review has demonstrated the utility of physical rehabilitation in HCT, its impact on cancer-related fatigue, and to outline the current state of the literature on these topics. The paper delves into a background of HCT. Cancer-related fatigue in HCT is then discussed and summarized, and the role that exercise plays in modifying such fatigue is outlined. We then outline the models and the impact that physical rehabilitation may play in HCT recipients.

Keywords

Stem cell transplantation; Cancer fatigue; Exercise; Rehabilitation program

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Introduction

Hematopoietic stem cell transplantation (HCT) is a procedure that has evolved substantially over the years to help treat multiple conditions, particularly hematologic malignancies. HCT can be very stressful on the body and often leaves patients weakened and quite debilitated. Supportive care measures have advanced to improve the quality of life and overall survival of HCT patients. Physical medicine and rehabilitation is gaining increased attention and is one key component of improved supportive care. New insight and research within the discipline have focused on fatigue, inflammation, exercise, and the development of structured rehabilitation programs to improve the musculoskeletal sequelae of HCT. The primary purpose of this review is to demonstrate the utility of physical rehabilitation in HCT, its impact on cancer-related fatigue, and to outline the current state of the literature on these topics. The paper first discusses the background of HCT. Cancer-related fatigue in HCT is then discussed and summarized, and the role that exercise plays in modifying such fatigue is outlined. We then outline the models and the impact that physical rehabilitation may play in HCT recipients.

Stem cell transplantation

HCT is a procedure used to treat and potentially cure a number of medical conditions, including leukemia, lymphoma, and myeloma, and inherited conditions such as thalassemia and sickle cell anemia. HCT was first described in humans in the medical literature in 1957 [1]. Generally, HCT may be broken down into autologous transplants or allogeneic transplants.

In autologous transplantation, a patient's stem cells (which have the potential to differentiate into new white cells, red blood cells, and platelets) are collected prior to high-dose chemotherapy. High-dose chemotherapy is then administered to destroy neoplastic cells. The high-dose chemotherapy damages the patients' ability to produce blood cells. This is rectified by reintroducing the previously collected stem cells back into the patients after the high-dose chemotherapy has been cleared from the body. This "rescues" their blood counts so that the patients recover in approximately 3 weeks from the time of chemotherapy until the time of blood count recovery.

In allogeneic transplantation, rather than collecting the patient's own stem cells, a donor's stem cells are collected instead. This adds the extra benefit of allowing for a graft-versus-tumor effect, whereby the newly acquired immune system of the donor attacks the patient's underlying abnormal condition or malignancy. Additional complications of allogeneic transplantation involve the risk of graft-versus-host disease (GVHD). GVHD causes the donor's cells to not only attack the underlying malignancy but the host's regular cells as well (such as the liver, gastrointestinal tract, or skin). To help prevent this, patients are placed on immunosuppressants to weaken the immune response of the donor cells. This also weakens the host immune system, increasing the risk of infection. To prevent infection, patients are placed on prophylactic antimicrobial agents. As a result, patients who undergo HCT are placed on many medications that are required to be taken daily, with numerous associated side effects.

In addition, both autologous and allogeneic HCT patients are at risk for anemia and thrombocytopenia, either from the therapy or related to their underlying condition. Of course, the musculoskeletal system may be affected by deconditioning and steroid myopathy. These issues may be compounded by peripheral neuropathy and psychological/emotional sequelae. Combined, these long-term issues may play a negative role in a patient's quality of life. In particular, fatigue is a significant issue that plagues patients.

All told, one can imagine that patients who undergo HCT have a great deal of stress placed on their bodies. Therefore, it is imperative that they maintain an optimal performance status before transplant, during the initial hospitalization, and through the months, sometimes years, which patients will be managed and followed. In those who undergo the HCT process and those who survive long afterwards, fatigue is a common complaint experienced by patients.

Cancer-related fatigue

Fatigue is the most common and one of the most devastating symptoms among patients with cancer. [2]. According to the National Comprehensive Cancer Network, cancer-related fatigue (CRF) is defined as a “persistent, subjective sense of physical, emotional, and/or cognitive exhaustion related to cancer or its treatment that is not proportional to recent activity” [3]. Fatigue has been rated as having a greater negative impact on quality of life than other cancer-related symptoms such as pain, depression, and nausea [4]. It is important to distinguish so-called healthy fatigue from CRF. Healthy fatigue is fatigue that is eventually relieved by rest and sleep. CRF is not proportional to recent activity and interferes with usual functioning. For example, patients with CRF will complain of difficulty with doing routine activities that previously did not cause any distress, such as laundry, running errands, or cooking. In fact, CRF has a negative impact on all areas of function, including mood, physical function, work performance, social interaction, family care, cognitive performance, school work, and community activities [5–7].

Fatigue is also very common among HCT patients. Table 1 reviews the literature on the correlation between fatigue and overall quality of life among survivors of HCT patients. In a study by Giellissen et al., it was estimated that severe fatigue occurs in 35 % of long-term transplant survivors (over 15 years out from transplant). Even in the short term (between 1 and 5 years out from transplant), there is a 41 % chance that severe fatigue occurs [8]. The authors could not conclude that one specific comorbidity caused more fatigue than others—only that comorbidities were in general more often associated with severe fatigue. Additionally, the authors also did not note a correlation between fatigue and hemoglobin level or medications.

The etiology of CRF is not entirely clear, although many potential factors may contribute to this symptom or may be a consequence of this syndrome. Potential factors include direct toxicity from chemotherapy and radiation therapy [30], the cancer itself [31], genetic vulnerability [32], hormonal changes [33], medication side effects [34], poor sleep [35], depression and anxiety [36], chronic stress, poor nutrition [37], loss of muscle mass and inactivity [38], and other chronic medical problems [39]. Inflammation related to inflammatory cytokines is increasingly being recognized as playing a key role in the genesis

of cancer-related fatigue. Basic research on neural-immune interactions has shown that pro-inflammatory cytokines can cause potent changes in behavior including reduced activity, fatigue, decreased social behavior, and cognitive dysfunction [30]. More debilitating levels of CRF have been associated with increased serum measurements of pro-inflammatory cytokines [40].

These recent findings may lead one to wonder what factors could be contributing to such fatigue among BMT patients. It may be that inflammation, which in essence is one of the critical factors related to GVHD, may be playing a role. If inflammation is a critical factor in the genesis of CRF, then one would assume that decreasing inflammation may be a key treatment as well.

Exercise in the treatment for cancer-related fatigue

Based on a recent Cochrane Database Systemic review, exercise may be regarded as beneficial for individuals with CRF, particularly during post-cancer therapy [41]. Further research is required to determine the optimal type, intensity, and timing of exercise intervention for mitigating CRF. Nevertheless, exercise has demonstrated significant improvements in multiple areas related to quality of life in addition to fatigue, including mood, bone health, sleep, body composition, functional capacity, and possibly survival among certain cancer survivors, including breast and colon.

Moreover, exercise has also demonstrated physiological and psychological improvement for HCT patients. For example, it has been shown that exercise improves physiologic outcomes after HCT [42]. Exercise has also been shown to reduce fatigue and some musculoskeletal symptoms in survivors [43, 44]. Lower performance status at the time of HCT has been associated with a lower survival and risk for GVHD [45]. Recently, there was a report of the benefits of exercise in mice that had undergone stem cell transplantation [46]. Despite the known benefits of exercise for cancer survivors, unfortunately an assessment of pre-diagnosis level of activity occurs in less than half of cancer survivors.

Pathophysiology of exercise's benefits

As discussed earlier, inflammation is believed to be a key contributor to CRF. In addition, exercise has been shown to decrease fatigue. The mechanism by which exercise decreases fatigue among cancer survivors has not yet been fully elucidated. However, a theoretical model for why exercise may serve as an important tool for CRF may be gleaned from recent developments from the general (i.e., non-cancer) exercise physiology literature. Table 2 presents a summary of the current literature assessing the role of physical rehabilitation and the effect on fatigue and quality of life in HCT.

Exercise has potent anti-inflammatory properties. There are several mechanisms by which this is believed to take place:

1. Exercise reduces visceral fat (i.e., “bad” fat). An increase in visceral fat is correlated with a higher production of pro-inflammatory cytokines such as TNF, IL-6, and leptin. For this reason, visceral fat is associated with increased all-cause mortality and the development of diabetes, cardiovascular disease, and dementia as

well as several cancers [61, 62]. Regular exercise can reduce waist circumference and reduce visceral fat—even in the absence of body weight reduction [63].

2. Exercise releases IL-6 from contracting muscle. Typically, IL-6 is associated as being a pro-inflammatory cytokine. However, the role of IL-6 may depend on the source where it is being produced. With exercise, the transient rise in IL-6 from muscle during exercise then leads to a subsequent rise in anti-inflammatory cytokines, such as IL-10 and IL-1 receptor antagonist [64].
3. Exercise increases the secretion of adrenal hormones such as cortisol, epinephrine, and norepinephrine, which have potent anti-inflammatory effects [65].
4. Exercise changes the phenotype of fat cells to produce less inflammation. M1-type macrophages are associated with the production of inflammatory cytokines and obesity [66]. With consistent exercise, there is a phenotypic switch of adipose tissue macrophages toward M2-type macrophages which produce anti-inflammatory cytokines.
5. Exercise may reduce inflammation via downregulation of toll-like receptors on monocytes and macrophages [67]. Activation of toll-like receptors results in increased production of pro-inflammatory cytokines. Other mechanisms are also believed to play a role in the anti-inflammatory effects of exercise.

We do not yet know the relative importance to each of these different anti-inflammatory mechanisms. However, the anti-inflammatory effects of exercise may explain why exercise is beneficial for CRF. These anti-inflammatory effects of exercise have generally not been well-studied in the cancer and palliative care setting. More studies are needed to address the optimal prescription of exercise to treat common cancer symptoms. This research includes studies assessing the type of exercise, frequency, duration, and intensity of the exercise, particularly in the setting of HCT recipients.

HCT rehabilitation programs

HCT patients can suffer from a multitude of complications which can have functional and medical consequences. A challenge is finding a way to successfully integrate rehabilitation in the setting of these medical complexities. From a systems-based approach, the rehabilitation of HCT patients can be divided into pre-transplant, peri-transplant, immediately post-transplant, and long-term survivors.

Pre-transplantation rehabilitation of the HCT patient

Many patients have had a significant decline in activity even before the transplant due to prior chemotherapy, radiation therapy, surgery, or other medical complications. Pre-transplant rehabilitation is important because a minimum level of performance may be required before transplant. Also, theoretically improving strength and cardiorespiratory reserves may benefit the patient after the transplant. These pre-transplant rehabilitation concepts have gone by several names including “preventative rehabilitation,” “prehabilitation,” and “buffering” [49, 68, 69]. An example of this concept would be a pre-HCT boot camp. Just as a military boot camp prepares soldiers to endure the challenges of combat, a pre-HCT boot camp could improve strength and cardiorespiratory reserves to

prepare patients for HCT. Challenges to the boot camp model include minimizing delays in transplantation and patient tolerance of exercise programs. Additionally, recent research has found that peri-transplant exercise program can be feasible and effective in improving aerobic capacity and strength [50, 70].

Immediately post-transplant rehabilitation

Post-HCT physical activity drops significantly when compared to pre-HCT physical activity [28]. This may be precipitated by factors such as fatigue. Also, the natural limitations of undergoing intense therapy in a hospital such as continuous connections to IVs, the need for close monitoring and observation of sophisticated infusions, and the limits of isolation due to neutropenic and contact precautions. Rehabilitation during this immediately post-transplant period involves maintaining function, reducing symptom burden, maintaining muscle mass, reducing the risk for pneumonia and atelectasis, and improving aerobic capacity. A typical post-HCT performance pattern is significant functional decline during and immediately after HCT followed by limited improvement [70]. It has also been found that HCT patients have a decline in voluntarily engaging in exercise activities [50]. Reduced exercise activity will exacerbate reduced functional performance. In the post-transplant setting, murine models show that exercise is important because it may impact survival [71].

Research suggests that structured exercise programs beyond simple encouragement are more effective in maintaining patient activity [49]. Post-HCT exercise/activity may incorporate group exercise programs, an intermittently supervised exercise program, keeping records of distance walked, and frequent individual physical/occupational therapy if indicated.

A physiatrist, also known as a physician who specialized in physical medicine and rehabilitation, helps restore optimal functional and quality of life to patients who have challenges in this arena as a result of illness or injury. A subspecialty of cancer rehabilitation (or onco-physiatry) is also emerging for physiatrists who have a special interest and skill set in the care of patients with cancer, including with problems such as cancer-related fatigue, cancer pain syndromes, and neuromusculoskeletal complications of cancer and its treatment. The central tenet of cancer rehabilitation is to help a person with cancer attain the maximal physical, social, psychological, and vocational functioning within the limits imposed by the disease and its treatment [72].

The Mayo Clinic developed a physiatry consult-based cancer rehabilitation model published in 1980. The cancer adaptation team (CAT) consisted of a physiatrist, physical therapist, occupational therapist, nurse, social worker, and chaplain. The team held daily meetings regarding patients and followed the patients while they were on the primary oncology service. Although there was no control group, they published results demonstrating improvements in the Karnofsky and Barthel Index scores of their patients [73, 74]. The CAT model is still being used at the Mayo Clinic today. At MD Anderson Cancer Center, a similar model called the mobile team has been used for several years. The mobile team consists of a physiatrist, physical therapist, occupational therapist, and nurse and also involves daily morning meetings to discuss patient cases. The mobile team can be thought of as mobile acute inpatient rehabilitation. Patients rehabilitate with the mobile team while on the primary acute care service. Mobile team patients can receive up to 1 h of physical

therapy and up to 1 h of occupational therapy daily depending on their therapy tolerance (so up to 2 h of therapy/day, this is in contrast to the 3 h of therapy/day in acute inpatient rehabilitation). The goals of the mobile team can vary depending on the patient. One goal of the mobile team is to address therapy tolerance. This information is useful in determining an appropriate rehabilitation destination for the patient. If a patient can tolerate 2 h/day of therapy without issue, it is likely that they could tolerate 3 h/day on acute inpatient rehabilitation. A second common goal for the mobile team is to overcome barriers to discharging the patient home such as family training, educating on the use of equipment, stair training, or how to transfer. The more intense therapy of the mobile team (versus the typical floor therapists) often times can achieve these goals while remaining on the primary acute care team. If successful, it may enable the patient to discharge home without transferring to another rehabilitation setting. It is also more efficient because patients can begin more intense rehabilitation while still on the acute care medical team's service. The CAT and mobile team are not used exclusively for HCT patients; however, they are very useful in this population given their medical fragility. Due to reimbursement models, the increased therapy provided to HCT patients in the mobile team/cancer adaptation team model may be cost-prohibitive in diagnosis-related group health care facilities.

Intermittently supervised exercise programs are used at many institutions where HCTs occur. However, the evidence is not yet clear about the most beneficial type or timing of exercise as an adjuvant intervention for patients on the HCT continuum [60]. At MD Anderson, it starts with patient education (pre-transplant preferred) regarding guidelines for exercise precautions including education on fatigue, orthostasis, and other complications. During the HCT hospitalization, patients undergo a self-performed exercise program, pedal exerciser, and frequent follow-up with a therapist who performs individual therapy with the patient. Group sessions also occur several times a week and are with a physical therapist, occupational therapist, or music therapist. In hospitals where development of large specialized teams for implementation of physical rehabilitation programming is out of reach, other smaller scale strategies may be used. Providing patients with handouts about the benefits of exercise and physical activity prior to HCT, connecting patients with community support programs at local fitness centers and cancer support programs after HCT, and designing a basic home-based exercise program for patients during the HCT continuum are feasible, inexpensive, and effective modes for delivering physical rehabilitation (and prehabilitation) to HCT patients. Table 3 provides example guidelines that could be given to HCT patients as part of a cancer rehabilitation program.

During the post-transplant period, patients cannot remain on the acute care service indefinitely. If the patient is unable to safely discharge home, a transfer to another rehabilitation setting may be required. This can present a challenging situation because of this patient population's medical fragility. One study showed that 41 % (61/147) of HCT inpatient rehabilitation admissions were transferred back to the primary acute care service [75]. Of those transferred back, 38 % (23/61) died after being transferred back. The top reasons for return to the primary team included infection (28 %), functional decline or inability to tolerate therapy (18 %), cardiac issues (10 %), mental status changes (10 %), gastrointestinal bleeding (7 %), completion of rehabilitation (3 %), brain hemorrhage (3 %), and leukemia treatment or recurrence (3 %). Significant or near-significant relationships

were found for platelet counts less than 43,000/mL ($p<.01$), creatinine greater than 0.9 mg/dL ($p<.01$), the presence of an antiviral agent ($p = .0501$), the presence of an antibacterial agent ($p=.0519$), the presence of an antifungal agent ($p<.05$), and a leukemia, lymphoma, or multiple myeloma diagnosis ($p<.05$). From this, a return to primary-bone marrow transplant scoring system (RTP-BMT) was developed. The RTP-BMT score is shown in Table 4. Future validation studies of the RTP-BMT score are needed. However, the RTP-BMT score could be useful to a physiatrist who is determining the best rehabilitation destination for a HCT patient. Patients with a high RTP-BMT score may benefit more from in-house rehabilitation where they are close to medical resources for acutely ill patients. Patients with a lower RTP-BMT score may be safe to transfer to an outside rehabilitation facility. Outside rehabilitation facilities are often freestanding and can be miles from the nearest intensive care unit or medical specialists. At skilled nursing facilities, patients are not typically seen daily by a physician. Transferring patients at high risk for medical complications to such facilities may create a dangerous situation for the patient.

The long-term HCT survivor

Cancer survivorship care continues to increase and is an area of tremendous growth in cancer rehabilitation. As time passes, the focus of these patients shifts from simply surviving the cancer to quality of life. Many long-term post-HCT cancer survivors suffer from impairments due to treatments and complications they received as demonstrated in Fig. 1. The bad news is that peripheral neuropathy, steroid myopathy, chronic fatigue, deconditioning, and lost muscle mass are common issues in this patient population. The good news is that many of these issues can be addressed by physiatry and rehabilitation. The long-term HCT survivor's rehabilitation will likely occur in an outpatient setting and may require months, years, or longer. Some patients will not be able to return to work and may require assistance applying for disability.

Despite an increased recognition of the importance of cancer rehabilitation and hematopoietic stem cell transplantation, barriers continue to exist. Unfortunately, physical medicine and rehabilitation is unavailable in many cancer centers [76]. When it is available, cancer rehabilitation is often underutilized due to a lack of awareness of its role and potential benefits [77–79]. Educating oncologists and other cancer health care professionals about the presence and capabilities of cancer rehabilitation is important.

The role of psycho-oncology and physiatry in HCT rehabilitation

The psychological aspects of survivorship must also be factored in, and mental rehabilitation may need to be focuses on. Psycho-oncology represents an area of multi-disciplinary interest (psychiatry, psychology, social worker, spiritual care, nursing, etc.) whose goals is to holistically improve the care of people affected by cancer and its treatment at all stages. Psycho-oncologists are also best equipped to evaluate the psychological, social, and behavioral factors that influence tumor progression and survival. As such, psycho-oncology would be an ideal and integral part of the rehabilitation team for patients undergoing SCT, when available, given the profound psychological and behavioral implications of this treatment process.

Conclusion

One of the key reasons for the improvement in quality of life and overall survival in HCT patients has been the significant progress made in the supportive care of such patients. In particular, strides in rehabilitating patients physically, with a focus on inflammation, fatigue, and exercise, will hopefully continue to improve patient lives. Rehabilitation of HCT patients can occur using a variety of models during the pre-transplant, immediately post-transplant, and long-term post-transplant phases.

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Fig. 1.
Impairments, disabilities, and handicaps of long-term HCT survivors

Table 1

Studies assessing fatigue and quality of life during and after HCT

Author	QOL index (only QOL measures listed)	Number of patients	Transplant type	Outcomes	Time frame	Other considerations
Gielissen et al. [8]	CIS-fatigue (fatigue severity) Impact of event scale-Dutch Version (coping with the experience of fatigue)	N = 98 (allo = 79; auto = 19)	Allo and auto	35 % of patients experienced severe fatigue (mean = 9.3 years after transplant)	Mean = 9.3 years post-HCT	
Bevans et al. [9]	SDS	N = 76	Allo only	-Fatigue, worry, and appetite change were the most prevalent across all study points -At day 100, 60 patients (90 %) reported fatigue as the most distressing symptom	Pre-HCT-day 100 post-HCT	Clustered symptoms
Boland et al. [10]	EORTC-QLQ-C30	N = 32 (allo = 3; auto = 29)	Allo and auto	-Fatigue and pain were the predominant symptoms negatively impacting physical functions	Median = 5.5 years post-HCT	
Cohen et al. [11]	FACT-BMT MDASI-BMT	N = 164 (allo = 102; auto = 62)	Allo and auto	-Physical weakness, sleep disturbance, lack of appetite, fatigue, and drowsiness were the five most severe symptoms across all time points	Pre-HCT-day 100 post-HCT	
Grulke et al. [12]	EORTC-QLQ-C30	–	Allo and auto	-Fatigue scores the highest in relation to all other symptom score -Over time, it decreases to the (high) pre-transplant level -Fatigue is a major concern persisting over time	–	Review article summarizing the use of the EORTC-QLQ-C30 in HCT
Hjermstad et al. [13]	EORTC-QLQ-C30; The Fatigue Questionnaire (FQ)	N = 248 (allo = 61; auto = 69; conventional chemo = 118)	Auto, allo, and conventional chemotherapy (no transplant)	-All patients reported more physical, mental and total fatigue relative to the general population	3–5 years post-HCT	
Kav et al. [14]	EORTC-QLQ-C30	N = 67	Auto only	-Financial difficulties, fatigue, sleeping problems, and pain were the factors most affecting QOL.	16.1 months post-HCT	
Larsen et al. [15]	SFID-SCT	N = 43 (allo = 17; auto = 26)	Allo and auto	-“Tiredness” was reported by >50 % of the patients at all time points -Tiredness was reported as “quite intense” or “very intense” 118 times	Admission for HCT discharge	

Author	QOL index (only QOL measures listed)	Number of patients	Transplant type	Outcomes	Time frame	Other considerations
Morishita et al. [16]	Piper Fatigue Scale	N = 83	Allo only	-Patients with sarcopenia experienced increased fatigue compared to patients without sarcopenia	At admission for HCT	
Mosher et al. [17]	FACT-BMT	N = 406 (allo = 29.1 %; auto = 60.3 %; missing = 10.6 %)	Allo and auto	-56 % of survivors reported persistent fatigue	1–3 years post-transplant (average 21 months since HCT)	
Andrýsowski et al. [18]	SCQ	N = 110 (allo = 13 %; auto = 87 %)	Allo and auto	-57 % of patients reported that “energy level” was a current concern -34 % reported that energy level was a past concern (not within the prior 30 days, but since HCT)	Average = 16.9 months post-HCT	
Bieri et al. [19]	EORTC-QLQ-C30	N = 124	Allo only	-Items differing in patients from the reference population were fatigue, dyspnea, sleep disturbances and financial impact ($p = 0.02$)	Median = 7 years	Reference population—age and gender comparable Norwegian population
Heinonen et al. [20]	FACT-BMT	N = 109	Allo only	-Females indicated worse emotional well-being and more fatigue than males -Females indicated more tiredness and less quality sleep	Mean = 54.5 months post-HCT	
Kopp et al. [21]	EORTC-QLQ-C30	N = 56 (allo = 40; auto = 16)	Allo and auto	-Significantly higher values in the symptom scales of fatigue, nausea and vomiting, pain, dyspnea, and appetite loss in those patients <1 year post-HCT	Mean group 1: 5.5 months Mean group 2: 59.2 months	Group 1: 1 year post-HCT; group 2: > 1 year post-HCT
Lee et al. [22]	Likert scales	N = 458 (allo = 201; auto = 114; synergistic = 5)	Allo and auto	-Patients were most likely to be bothered by fatigue, financial problems, and sexual difficulty -Similar between auto and allo	6 months, 12 months, and 24 months post-HCT	
Bevans et al. [23]	SF-36, FACT-BMT, FACT-G	N = 78	Allo	-By 2 years post-HCT, patients experienced fewer role limitations, more satisfaction with their personal life and less fatigue.	Prospective: pre-HCT—2 years post-HCT	Reduced intensity conditioning only
Rischer et al. [24]	EORTC-QLQ-C30	N = 50 (allo = 39; auto = 11)	Allo and auto	-Increase in fatigue and a decrease in physical functioning highly correlated with sleep disturbance	Prospective: admit-day 100 post-HCT	Primary outcome was sleep quality

Author	QOL index (only QOL measures listed)	Number of patients	Transplant type	Outcomes	Time frame	Other considerations
Sherman et al. [25]	FACT-BMT	N = 94	Auto only	-95 % of patients reported at least moderate fatigue at stem cell collection	At stem cell collection	Myeloma only
Andrykowski et al. [26]	Symptom Experience Report	N = 200 (allo = 93; auto = 107)	Allo and auto	-“Feeling tired” was the most frequently reported symptom (78 %) -Fatigue, dyspnea, and sleep disturbance were most frequently reported symptom -Fatigue and dyspnea decreased in patients more than 5 years post-HCT -In patients with chronic GVHD, more fatigue was reported	Mean = 41 months post-HCT	
Worel et al. [27]	EORTC-QLQ-C30	N = 155	Allo only		2–5 years post-HCT	
Hacker et al. [28]	Single item global report; EORTC-QLQ-C30	N = 20 (allo = 7; auto = 10)	Allo and auto	-Pre-HCT, patients rated their fatigue as “mild” -Post-HCT, patients rated their fatigue as “moderate”–“severe”	Pre-HCT and post-HCT	Three patients did not undergo transplant
Wood et al. [29]	PRO-CTCAE	N = 32; (allo = 22; auto = 10)	Allo and auto	Fatigue and insomnia were the most commonly reported symptoms at all time points in both groups	Pre-HCT-Day 100 post-HCT	

Allo allogeneic, *Auto* autologous, *BFI* Brief Fatigue Inventory, *CIS* Fatigue Checklist of Individual Strength-Fatigue subscale, *CG* control group, *EORTC-QLQ* European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, *FACT* Functional Assessment of Cancer Therapy, *MDASI*/MD Anderson Symptom Inventory, *PRO-CTACE* Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events, *QOL* quality of life, *SDS* Symptom Distress Scale, *SF1D-SCT* Symptom Frequency, Intensity, and Distress questionnaire for Stem Cell Transplant

The role of physical rehabilitation in human adults undergoing HCT—effects on fatigue

Table 2

Author	QOL Index (only fatigue index listed)	N; transplant type; N, TG	Study design and information	Outcomes	Notes
Baumann et al. [43]	EORTC-QLQ-C30	N = 64; auto = 18; allo = 46; TG = 24	-Design: prospective intervention, 2 arms -TG received aerobic exercise therapy twice a day during aplasia and once a day during engraftment -TG received ADL training daily during conditioning, not during aplasia, and daily during engraftment -CG received gymnastics, massages, stretches and coordination training -Study duration: study start: day-6. Study end: 1 day prior to discharge	-Endurance decreased in CT and stayed the same in TG -Strength declined in both groups -TG had improved quality of life -CG experienced greater fatigue than TG which had no change from baseline	-Contraindications: -Platelets <10–20 n/l -Pain, somnolence, confusion, dizziness, infection, nausea, and/or vomiting -Hgb <8 g/100 mL -Fever >38.0 °C -Days received cardiac or nephrotoxic chemo
Kim et al. [47]	Revised Piper Fatigue Scale	N = 35; allo only TG = 18	-Design: prospective intervention, 2 arms -TG (n = 14) received 30 min of guided relaxation breathing and exercise (stretching) six times per week -CG received standard of care	-TG experienced decreased fatigue compared to CG	
Coleman et al. [48]	Profile of Mood States	N = 24; tandem transplant TG = 14	-Design: prospective intervention, 2 arms -TG (n = 14): home-based combination strength and aerobic intervention for 6 months -CG: standard of care	-Only statistically significant change was a positive effect on lean body mass -There was a trend toward significance for decreasing fatigue and mood disturbance -TG maintained lean mass, gained strength, and lost fewer minutes during treadmill testing	Exercise occurred at home between transplants
Courneya et al. [49]	FACT-BMT	N = 25; auto only	-Design: prospective observational, 1 arm	-Significantly reduced physical activity from pre-diagnosis to post-diagnosis -Absolute levels of post-HCT exercise were very low -Patients experienced decreases in overall wellbeing over the weeks of hospitalization	No intervention
Hacker et al. [28]	Single item global report; EORTC-QLQ-C30	N = 20; allo-7; auto-10	-Design: prospective observational, 1 arm -Direct measurement of physical activity with tri-axial accelerometer for three consecutive days before and after HCT	-Patients performed more defined periods of physical activity pre-HCT -Post-HCT physical activity over the course of 24 h stayed the same with less clearly defined periods -Pre-HCT, patients rated their fatigue as “mild” -Post-HCT, patients rated their fatigue as “moderate” – “severe”	Three patients did not receive HCT due to complications
Hacker et al. [50]	EORTC-QLQ-C30	N = 10; allo = 7, auto = 3	-Design: pilot study-prospective intervention, 1 arm -Strength training intervention for 6 weeks after HCT	-Sample size is too small for any conclusions -Feasible programming	

Author	QOL Index (only fatigue index listed)	N; transplant type; N, TG	Study design and information	Outcomes	Notes
Jarden et al. [51]	FACT-An	N = 42; allo only TG = 21	-Moderate, progressive, resistance to upper and lower body and abdominals -Moderate, progressive, resistance to upper and lower body and abdominals -8 pre-selected exercises -Accelerometer measured physical activity for 5 days -Design: prospective intervention, 2 arms -TG: inpatient exercise 1 h/5 days/week from admit to discharge -TG: stationary cycling, stretching, resistance training, progressive relaxation, and psychoeducation -CT: standard of care with physiotherapy following allo-HCT	-TG experienced significant improvements in predicted VO_{2max} and strength -The FACT-An favored TG but did not reach significance.	Contraindications: -Fever $>38^{\circ}C$ -Hgb <5 g/100 mL -ANC $<0.05 \times 10^9/L$ -Platelets $<20 \times 10^9/L$
Knols et al. [52]	EORTC-QLQ-C30; FACT-An	N = 131; allo = 51; auto; 80 TG = 64	-Design: prospective intervention, 2 arms TG: 12 week supervised progressive strength and cycling (cardio max time 20 min) program performed two times per week	-Mean time after HCT = 79 days -TG experienced improvements in cardio fitness and strength -No significant changes in fatigue or QOL -Author sites that changes in PROs could be affected by the small dose of cardio exercise	
Mello et al. [53]	None	N = 18; allo only TG = 9	-Design: prospective intervention, 2 arms -Time frame: pre-HCT—16 weeks post-HCT -TG: daily strength training on weekdays, initiated during inpatient period (total duration 40 min) CG: standard of care	-Both CG and TG were similar at baseline -At post-BMT both had declined -At 6 weeks, post-BMT-TG had higher strength values in all groups -Patients with sarcopenia had higher levels of fatigue	-No direct measure of fatigue
Morishita et al. [16]	Piper Fatigue Scale	N = 164; allo only	-Design: prospective observational, 1 arm -Time frame: pre-HCT -No intervention	-Patients with sarcopenia had higher levels of fatigue	-No intervention
Tonosaki [54]	Japanese Cancer Fatigue Scale	N = 19; cord blood = 15; allo = 4	-Design: prospective observational, 1 arm -24 h step count at discharge post-HCT (inpatient) and in clinic (outpatient) -Leg strength assessment -No intervention	-Patients who were active during hospitalization were better able to maintain activity at discharge -Plantar flexion strength positively influenced step count -Compared with fatigue during hospitalization, physical fatigue during homestay period decreased significantly -Subjects with lower BMI had more fatigue	-No intervention
Wilson et al. [44]	Fatigue symptom index	N = 17; auto = 13; allo = 4	-Design: prospective intervention, 1 arm -Mean time post-HCT = 16.9 months -Sedentary participants (no PA for at least 1 month) -Home-based aerobic exercise program -20–40 min activity in a target HR zone	-Participants reported modest fatigue at baseline -Symptom severity improved significantly -Aerobic fitness improved significantly	Contraindications: -Known cardiovascular disease -Hypothyroidism -Temp $>38^{\circ}C$ -Metastatic bone disease involving lower extremities -BMI <18 kg/m ² -Hgb <10 g/dL -ANC $<1 \times 10^9/L$

Author	QOL Index (only fatigue index listed)	N; transplant type; N, TG	Study design and information	Outcomes	Notes
Carlson et al. [55]	FACT-F, BFI	N = 12; allo only	-Design: prospective intervention, 1 arm -Median time post-HCT = 39 months -16 week intervention; 3 cycling workouts per week corresponding to different levels on VT	-Participants had high fatigue scores at baseline -Scores on FACT-F and BFI both changed significantly in the direction of less fatigue after the intervention -Fitness improved	-Platelets $<30 \times 10^9/L$
Dimeo et al. [56]	None	N = 66; auto only	-Design: prospective intervention, 1 arm -Patients in hospital for HCT -Daily aerobic exercise intervention -Treadmill walking in an interval pattern for 33 min (15 min of high intensity training) -3 min high intervals were 70 % of HRmax	-Daily aerobic training may help preserve the physical performance status of patients undergoing HCT	-No fatigue measures -Contraindications: -Hgb -Nutrition status -Infection -No specific parameters indicated
Dimeo et al. [57]	None	N = 10; auto only TG = 33	-Design: prospective intervention, 2 arms -TG received daily aerobic program during hospitalization for HCT -Patients biked in bed for 30 min/day at 50 % HRR (biking performed in 1 min/1 min intervals) -CG received SOC	-Loss of physical performance was 27 % higher in the CG -Duration of hospitalization was shorter for TG	-Contraindications: -Fever $>37.5^\circ C$ -Platelets $>10 \times 10^9/L$ -Infection -No direct measure of fatigue
Dimeo et al. [58]	None	N = 10	-Design: prospective intervention, 1 arm -6 week treadmill walking program -Average 30 days post-HCT	-Significant performance improvement -Conclusion: fatigue and loss of physical performance can be ameliorated by rehabilitation	-No direct measure of fatigue
Hayes et al. [59]	CARES (QOL)	N = 12; auto only TG = 6	-Design: prospective intervention; 2 arms -TG: 20–40 min moderate intensity aerobic and strength training program performed three times per week for 3 months after HCT -TG: training zones calculated by %HRmax -CG: progressive stretching program	-Regardless of participation in exercise program, a 3 month recovery period improved QOL -TG reported fewer and less severe problems (health) -TG reported improved QOL compared to CG -Those experiencing a higher level of fitness were more likely to experience higher QOL	-No direct measure of fatigue -QOL measure only
Wiskemann et al. [60]	POMS; EORTC-QLQ-C30	N = 105; allo only TG = 52	-Design: prospective intervention, 2 arms -TG: started exercise prior to HCT, continued during HCT, and for 6–8 weeks post-HCT -TG: 3 endurance (20–40 min; moderate) and 2 strength (8–20 reps, 2–3 sets; upper and lower body) sessions per week -TG: patients kept an exercise log -CG: informed that moderate activity is favorable, given pedometers, offered PT up to three times per week during HCT	-Patients in TG had less fatigue at all time points -Patients in TG had improved physical capacity -Patients in TG had improved functioning, anger/hostility, pain and global distress	-Contraindications: -Fever $>38^\circ C$ -Severe pain -Nausea -Dizziness -Platelets $<10,000/\mu L$ -Hgb $<8 g/dL$

Table 3

Example of cancer rehabilitation patient guidelines

As a part of your Oncology Rehabilitation Program, please perform the exercises and activities as directed by your therapist. Please follow these basic guidelines when participating in your program:	
1.	It is important to breathe normally during exercise. Do not hold your breath during exercise or other activities. Holding your breath places a strain on your heart and can increase your risk for bleeding.
2.	Sudden bursts of activity should be avoided. For example, jumping up to answer the phone or hurrying to the restroom may increase your risk of falling.
Check with your nurse before leaving your room to see if you need to wear a mask or have your IV disconnected. Also, check with your nurse before doing any out of bed activities. There may be times when you need to stay in bed for your medical treatment.	
Precautions: Do not exercise or walk and notify your nurse immediately if	
•	You have any shortness of breath
•	You are experiencing any increased pain
•	You are unusually tired or have sudden weakness
•	You have a rapid heart rate or heart palpitations
•	You are experiencing any new difficulty with balance
•	You are experiencing any dizziness

Table 4

RTP-BMT index cumulative values based on cut points for five factors and the percentage and relative risk grouping of bone marrow transplant rehabilitation patients' return to primary acute care service [75]

Did patient return to primary acute care service?			Probability of return to primary acute care service	Probability of return to primary acute care service by BMT-RTP Index Group
RTP-BMT Index *	No	Yes	%	
0	3	0	0.0225	0.0438
1	6	0	0.0537	
2	13	3	0.1230	0.1960
3	24	7	0.2573	
4	27	24	0.4611	0.5648
5	13	27	0.6788	

*Wald test for the overall model=20.627 ($p = <.0001$); Unit Odds Ratios (per unit change in regressor) = 0.404, CI [0.266, 0.583]

Antifungal present = 1; not present = 0

Antibacterial present = 1; not present = 0

Platelet count LESS than 43,000 per microliter (μ L) = 1; 43 K/uL or GREATER = 0

Creatinine GREATER than .9 (milligram/deciliter, mg/dL) = 1; .9 mg/dL or LESS = 0

RTP-BMT return to primary-bone marrow transplant index

* Antiviral present = 1; not present = 0