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[Review]

Effect of rehabilitation in patients undergoing hematopoietic stem cell transplantation

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Abstract

Patients undergoing hematopoietic stem cell transplantation (HSCT) tend to experience decline in physical function, mental function, and quality of life (QOL) after HSCT due to low activity caused by adverse reactions to chemotherapy used in pre-transplantation treatment and post-transplant complications. Rehabilitation for HSCT patients is effective in preventing decline in physical function, reducing fatigue, and improving QOL. A combination of aerobic exercise and strength training is recommended for exercise therapy. Risk management is also important in the implementation of exercise therapy, and the exercise intensity should be determined according to the presence of anemia, low platelet counts, or post-transplant complications. On the other hand, post-transplant complications can decrease the patient's motivation and daily activity level. A multidisciplinary approach, which includes physicians and nurses, is important to achieve early discharge from the hospital and as quick a return to society as possible.

Key words : Hematopoietic stem cell transplantation, rehabilitation, exercise therapy, physical function

Introduction

Hematopoietic stem cell transplantation (HSCT) is a curative treatment for hematopoietic malignancy.[1] In Japan, more than 5,000 HSCTs (both autologous and allogeneic) have been performed annually in recent years ; in FY2020, the total number of transplants was 6,076.[2] Patients who undergo HSCT experience reduced physical activity due to chemotherapy and/or total body irradiation used for pre-transplant treatment, as well as post-transplant complications. As a result, physical functions such as muscle strength and endurance, activities of daily living (ADL), and quality of life (QOL) are reduced.[3-5] Rehabilitation is useful for improving low physical activity, motor disorders, fatigue, and QOL associated with HSCT treatment.[6-8]

Historically, the first report on HSCT rehabilitation was in 1986, when Cunningham *et al.*[9] conducted exercise therapy in patients with acute leukemia after transplantation, and reported its effectiveness. Subsequently, reports on exercise therapy before and after transplantation began to increase from the 1990s onward. In recent years, it has been reported to be safe and feasible for rehabilitation performed prior to HSCT admission.[10,11]

This review provides an overview of (mainly allogeneic) HSCT rehabilitation, and demonstrates its effectiveness.

The benefit of exercise therapy in HSCT patients

Regarding the benefits of exercise therapy in HSCT patients, physical exercise, including aerobic exercise, resistance training, and relaxing stretching exercises, has been shown to positively affect physiological, psychological, and psychosocial health.[12]

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A meta-analysis by Liang *et al.*[13] reported that exercise therapy has a positive impact on lower extremity muscle strength, fatigue, and QOL. They also concluded that the appropriate time to begin exercise therapy for transplant recipients is before HSCT.[13]

Pulmonary exercise in allogeneic HSCT recipients is effective in improving 6-minute walking distance (6MWD) as well as respiratory muscle strength (maximal inspiratory pressure, maximal expiratory pressure).[14] In this study, inspiratory muscle training was performed using a pressure threshold-loading device for strengthening primarily the diaphragm and rib cage muscles.

With respect to changes in muscle mass after allogeneic HSCT, it has been reported that decreases in muscle mass observed approximately 6 weeks after transplantation are greater in the central areas, such as the upper arms, thighs and trunk, than in the peripheral areas, such as the forearms and lower legs.[4]

With regard to gender differences in physical function and QOL after allogeneic HSCT, it has been reported that grip strength and muscle mass declined more in men than in women.[15] On the other hand, women have been reported to experience a greater decline in QOL than men.[16] Furthermore, male patients tend to experience decreased muscle strength, while female patients tend to experience decreased QOL.

Regarding the effects of exercise and nutritional therapy on physical function and QOL, Rupnik *et al.*[17] reported that exercise and nutritional therapy (supplement of whey protein ; 0.3-0.4 g/kg) improved grip strength, 6MWD, and QOL in pre-HSCT patients. In contrast, for the HSCT hospitalization, Jabbour *et al.*[18] examined changes in handgrip strength in two groups, an exercise and nutrition intervention group (30-35 kcal/kg and 1.5 g/kg protein), and a standard-care group, and reported no differences between them. The effects of exercise and nutritional interventions in HSCT patients on post-transplant muscle strength, endurance, and QOL are not yet clear.

Exercise therapy in allogeneic HSCT patients also has a positive impact on post-discharge survival.[19] Jones *et al.*[20] reported that a 6MWD before transplantation of ≥ 400 m provided incremental information on the prediction of overall survival with adjustment of age. In contrast, a 6MWD of < 400 m before transplantation and a decrease in 6MWD distance before and after transplantation are associated with a high risk of non-relapse mortality after allogeneic HSCT.[20]

Exercise therapy in HSCT recipients is thought to have a positive impact on the maintenance of physical function, QOL, and survival after transplantation.

Allogeneic HSCT treatment

Allogeneic HSCT is a treatment in which the recipient undergoes high-dose chemotherapy and/or total body irradiation as pre-transplant treatments, followed by intravenous administration of donor hematopoietic stem cells. The recipient's blood cells (white blood cells [WBCs], red blood cells, and platelet) decline after transplantation due to pre-transplant treatments. The recipient-derived WBCs are replaced by donor-derived WBCs.[21] In general, WBC engraftment is achieved when three consecutive neutrophil counts of 500 /μL or more are observed.[22] HSCT procedures are performed in a clean room that is class 100-10,000 (International Organization for Standardization [ISO] Class 5-7) according to U.S. federal standards. The patients stay in the clean room until WBC engraftment. After allogeneic HSCT, the patients may experience a variety of side effects and complications. The side effects related to pre-transplant treatments include infections, anemia, and bleeding due to decreased blood cell counts, as well as mucous membrane disorders.[23,24] Complications after WBC engraftment include graft-versus-host disease (GvHD) and infections due to immune dysfunction. The expected length of hospitalization is a few months, but depending on the severity of complications, a prolonged hospital stay may be required.

Rehabilitation

HSCT rehabilitation can be divided into three major periods : pre-rehabilitation, inpatient rehabilitation, and outpatient rehabilitation (Fig. 1).[25] During hospitalization for HSCT, rehabilitation can be further divided into three periods (admission to HSCT, HSCT to engraftment, and engraftment to discharge). Rehabilitation during hospitalization should be performed by setting appropriate goals for each of these periods (Phase 2-4) [Fig. 2, 3].

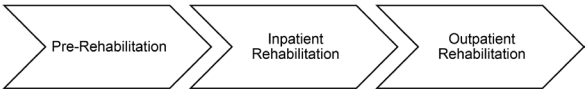

Fig. 1. HSCT rehabilitation pathway.

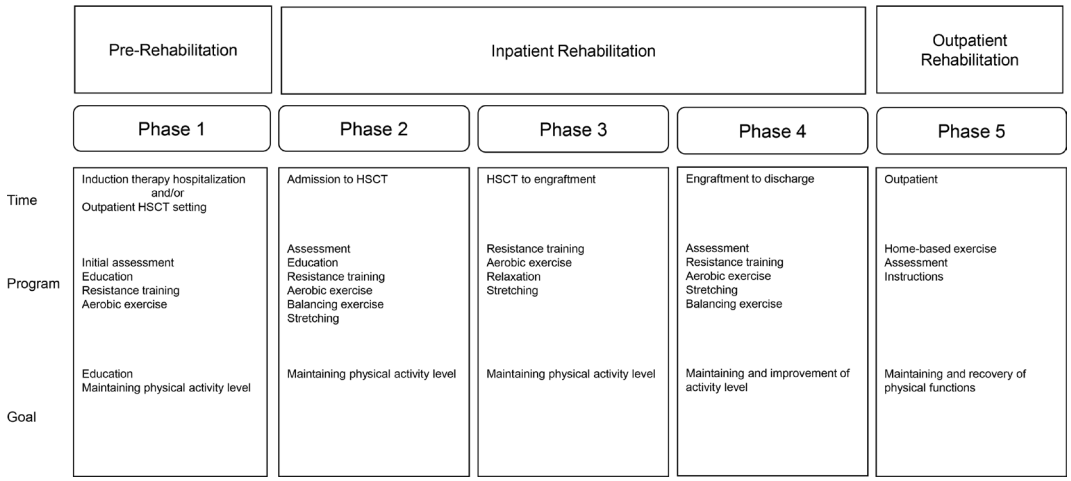

Fig. 2. Details of the HSCT physical therapy pathway.

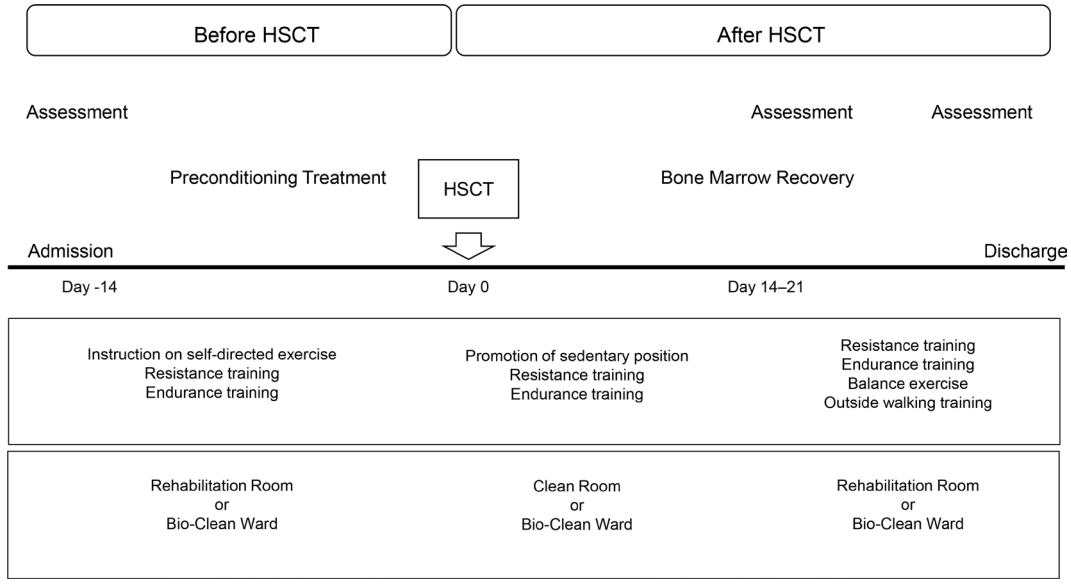

Fig. 3. HSCT rehabilitation protocol.

Assessment

Assessment during hospitalization for HSCT is generally performed before HSCT, after HSCT, and at the time of discharge (Fig. 2, 3). After HSCT, it is often difficult to perform all assessments due to poor physical condition, fatigue, and intravenous lines. Therefore, assessment is sometimes only performed before HSCT and at the time of discharge.[4)]

Pre-HSCT assessments are performed promptly after HSCT admission, and post-HSCT assessments are performed after WBC engraftment or when the patient is allowed to move to the rehabilitation room. The assessment at discharge is performed approximately one week prior to the date of discharge (Fig. 3).

Assessment items

Physical function assessment includes muscle strength, exercise tolerance, walking ability, flexibility, and balance.[3-5,10)] Body composition is assessed by measuring body weight and muscle mass.[4)] Muscle mass is generally measured using a bioelectrical impedance analysis (BIA) method, which is a noninvasive method.[26)] Other assessments, such as those assessing ADLs, fatigue, anxiety, and QOL, should also be performed. For QOL assessments, the Medical Outcome Study 36-item Short Form Health Survey[16,27)] and the European Organization for Research and Treatment of Cancer QLQ-C30[13,28)] are often used, but a license is required to perform

Table 1. Physical Therapy Assessment

Physical Function	
Strength	Upper extremity : Handgrip strength Lower extremity : Knee Extension Strength (hand dynamometer) 30-S chair stand test, 5 times sit to stand test
Exercise tolerance	6-min walking test (6MWT)
Balance	Standing on one leg time
Walking ability	Timed-Up & Go test (TUG)
Physical activity	Steps (pedometer)
Body Composition	
Muscle mass	Dual energy X-ray absorptiometry (DEXA) Magnetic resonance imaging (MRI) Computed tomography (CT) Bioelectrical impedance analysis (BIA)
Body weight	Body scale
Circumference	Four extremity circumference
Others	
Quality of life	SF-36, EORTC QLQ-C30, FACT-BMT
Depression	Self Depression Scale (SDS), Hospital anxiety depression scale (HADS)
Fatigue	Cancer Fatigue Scale (CFS), Brief Fatigue Inventory (BFI)

Abbreviations ; SF-36 : Medical Outcome Study 36-item Short Form Health Survey. EORTC QLQ-C30 : The European Organization for Research and Treatment of Cancer QLQ-C30. FACT-BMT : Functional Assessment of Cancer Therapy - Bone Marrow Transplantation.

these assessments. Typical assessment items are listed in Table 1.

Exercise therapy

It is recommended that exercise therapy consists of a combination of aerobic exercise and strength training.[29] Recent rehabilitation interventions before and after HSCT are shown in Table 2. Exercise therapy for HSCT recipients in Japan[4,5,30,35] is based on a frequency of five times a week for both aerobic exercise and strength training, while in other countries (e.g., Europe, the United States and Canada.[10,31-34]), the frequency of strength training varies mildly from two to five times a week (Table 2). However, the intensity of the exercise program is generally similar for strength training (Borg scale 13-16) and aerobic exercise (Karvonen method, 40-60% of maximum heart rate [HR]).

Stretching

Stretching serves a warm-up and cool-down role for exercise. It is mainly performed on the large muscle groups of the upper and lower extremities, as well as the trunk. It is recommended that stretching exercises should be performed daily.[36]

Strength training

The intensity of strength training can be usefully determined using one Repetition Maximum (1RM) method[37] or the Borg scale.[38] 1RM is the maximal amount of weight that a person can possibly lift for one repetition. The intensity of strength training is recommended at ≥ 60% of 1RM and 8-12 repetitions per set in healthy adults to increase muscular strength.[39] When using the 1RM method for HSCT patients, 60-80% of 1RM is used as an index.[37,40] Rate of Perceived Exertion (RPE) is a numerical way to measure the level of exertion a person feels during exercise. The Borg Scale is an index that quantifies the ranges of RPE on a scale of 6-20, where 6 means "no exertion at all" and 20 means "maximal exertion." When using the Borg Scale, the target intensity for exercise is "fairly light" to "hard" on a scale of 10-16.[41] In HSCT patients, there is a relationship between strength training intensity and the Borg Scale, with the Borg rating increasing as the intensity of exercise increases.[42] During hospitalization, before HSCT or near discharge from the hospital, the program should be adjusted and implemented with a target score of 13-16 (somewhat hard to hard) if there are no complications and 10-13 (fairly light to somewhat hard), if there are complications. It is important to select a program that primarily uses large muscle groups and targets the upper extremities, lower extremities and trunk. Resistance bands (upper and lower limb

Table 2. Physical therapy intervention

Study	Type	Frequency	Time	Intensity
J Wiskemann *et al.* 2010 [10], Germany	Aerobic	3–5 times a week		Borg Scale 12–14
	Strength	2 times a week		Borg Scale 14–16
T Takekiyo *et al.* 2015 [4], Japan	Aerobic	5 times a week 20–40 min/day	10–15 min	60% of maximal heart rate
	Strength		10–15 min	Borg scale 10–13
S Morishita *et al.* 2017 [30], Japan	Aerobic / Strength	5 days/week	20–40 min	
ED Hacker *et al.* 2017 [31], USA	Strength	3 times a week		Borg scale 13
A Ishikawa *et al.* 2019 [5], Japan	Aerobic	5 times a week	up to 30 min	60% of heart rate reserve
	Strength	5 times a week		
A Pah36l *et al.* 2020 [32], Germany	Strength	daily	20 min	Borg Scale 14–16
DS Mina *et al.* 2020 [33], Canada	Aerobic	3 times a week	10–30 min	60% of the heart rate reserve
	Strength		10–15 min	1–2 sets of 4–6 repetitions per exercise using the participant's exercise bands
A Kisch *et al.* 2020 [34], Sweden	Aerobic	5 times a week	20–30 min	Based on the patients' own performance and health status.
	Strength	5 times a week		
R Hamada *et al.* 2021 [35], Japan	Aerobic	5 times a week	20–40 min	40% of the maximum heart rate
	Strength			Borg scale "somewhat hard"

muscles) and step climbing using a 10–20 cm step (lower limb muscles) can also be used for strength training. Strength training should be performed two or three times per week.[29,36,43)]

Endurance training

Endurance training is performed using the Karvonen method[44)] or Borg Scale. The Karvonen method is a formula for calculating the target HR during exercise and is one of the indices used to set the intensity of endurance training. The formula is (220−age− resting HR) × intensity (%) + resting HR[44,45)]. Endurance training is recommended for healthy adults at 64–76% of maximum HR, or "somewhat hard" on the Borg scale[39)]. When using Karvonen method, the intensity of endurance training for HSCT patient is indexed at 60% of the maximum HR.[4,5,32)] Exercise tolerance is also associated with the Borg Scale, and HR during exercise tolerance tests is positively correlated with the Borg Scale.[42)] The Borg Scale is also useful for endurance training ; the target score for exercise intensity should be 12–14. Endurance training involves the use of a bicycle ergometer and walking down a corridor. Endurance training should be performed throughout the hospitalization period. Aerobic exercise is recommended to be performed 3–5 days per week, for a weekly total of at least 150 minutes.[29,36,43)]

Balance exercises

Balance exercises may be performed in a seated position with a balance disc or exercise ball. Standing exercises may also be useful. These exercises are useful in preventing falls and should be practiced throughout hospitalization.

Self-directed exercise

It is important to provide patients with self-directed exercise instructions to maintain daily activity levels. The exercise program should include exercises that can be performed in bed, in a sitting position, or in a standing position. Risk management during self-directed exercise is also necessary. During the period of myelosuppression, patients should be aware of anemia, thrombocytopenia, and falls.

Approach to exercise therapy

Phase 1. Pre-rehabilitation

The physical function of HSCT patients is already impaired prior to HSCT.[46] In addition, patients experiencing sarcopenia prior to HSCT experience decreased muscle strength and are generally more fatigued than non-sarcopenic patients.[47] Furthermore, the QOL of patients with sarcopenia has been found to be lower than that of patients without sarcopenia.[47]

Recently, the safety and feasibility of exercise therapy initiated prior to HSCT have been reported.[11] Exercise therapy should be started as early as possible after diagnosis of hematological disease to prevent pre-transplant physical function decline. Rupnik *et al.*[17] reported that the exercise prescription included 20-30 min of aerobic exercises at least 4 days per week and 10-20 min of strength exercises at least 3 days per week.

In the "pre-rehabilitation" period, an initial assessment is performed and the goal is to maintain physical activity (Fig. 2).

Phase 2. Admission to HSCT

At the start of exercise therapy during the HSCT inpatient period, the need for exercise therapy, an exercise program, self-directed exercise, and handling of complications should be fully explained. Regimen-related toxicity (RRT), such as nausea and diarrhea caused by preconditioning treatment, makes rehabilitation difficult for many patients. If RRT is observed, low-intensity interventions such as stretching and relaxation should be continued. In terms of physical activity, the total number of daily steps and the proportion of activity performed at 1.6-2.9 metabolic equivalents (METs) and > 3.0 METs were positively correlated with the 6 min walk distance.[30] The physical therapist should also be aware of the importance of maintaining activity in their approach, because maintaining physical activity can prevent decline in physical function after transplantation. During the preconditioning treatment period, the patient is often in relatively good physical condition ; thus, the physical therapist should focus on endurance training as much as possible (Fig. 2,3).

Phase 3. The day of HSCT to engraftment

On the day of HSCT, exercise therapy should be continued if possible. After HSCT, RRT is observed, making it difficult for patients to maintain physical activity. It is also important for the therapist to encourage the patient to continue stretching and promote sitting alone even when they are experiencing nausea, diarrhea, and fever (except for body temperatures over 38°C[4]), with a full explanation on why it is important. The goals of rehabilitation intervention during this period are to maintain the patient's ADLs and to continue exercise therapy, even for short periods of time. Even if rehabilitation cannot be performed, it is also important to continue to evaluate patients' movements such as basic activities (sitting and standing up) and walking to the toilet. During the period of low blood cell counts before engraftment, it is necessary to thoroughly manage the risks when performing exercise. Patients are also encouraged to manage their own risk by the attending physician, nurse or physical therapist, by explaining to them the precautions they should take in performing daily activities when anemia and low platelet counts are observed. Particular attention should be paid to the prevention of head bruising and falls when platelets are low. During the period of myelosuppression, the patient is susceptible to infection, so the therapist should pay close attention to infectious diseases and continue exercise intervention (Fig. 2, 3).

Phase 4. Engraftment to discharge from the hospital

After WBC engraftment, patients may experience a variety of symptoms, including difficulty eating, persistent fatigue, and persistent diarrhea due to GvHD.[13,48] Fatigue is also a significant factor that can limit the effectiveness of exercise therapy.[48] When these symptoms are observed, rehabilitation becomes difficult and patients may need assistance with ADL. It is important to maintain the patient's activity level by continuing daily exercise, even if only for short periods of time, if possible.

Many patients who are hospitalized for an extended period of time become less motivated to be active. Positive feedback from the therapist on improvements such as muscle strength, endurance, and activity level may lead to an improvement in the patient's motivation.

Falls are also a concern in long-term hospitalization. They are reported to occur more frequently after engraftment than before engraftment, and are related to the use of opioids and lower limb muscle weakness.[49] Patients may have difficulty walking due to bed rest caused by GvHD (especially in the gastrointestinal) or viral infections after HSCT, so daily assessment and appropriate movement instruction (particular measures to prevent falls) are

important.

At the time of discharge from hospital, the ability to move (walk) is the main concern, but it is also necessary to confirm that the patient is able to perform the activities necessary for living at home. Especially when the ability to climb steps and stairs is necessary to return home, such exercise should be continued from an early stage.

In this phase, the goals of exercise therapy are to restore decreased physical function and ADLs, and discharge from the hospital (Fig. 2, 3).

Phase 5. Outpatient rehabilitation

In Japan, many HSCT facilities provide rehabilitation during HSCT hospitalization, but after discharge from the hospital, patients are left to perform voluntary activities on their own. Therefore, prior to discharge, patients need to be instructed on the exercises that they should do at home (Fig. 2). In recent years, support has been provided by the Long-term Follow-up (LTFU) outpatient clinic. LTFU is carried out at 3 months, 6 months and 1 year following discharge, then every year thereafter.[50] The role of the physical therapist in the LTFU is to conduct an assessment, understand the patient's current physical function and activity level based on the assessment results, and adjust the patient's exercise program accordingly.

The recommended amount of physical activity after discharge from the hospital is aerobic exercise for a weekly total of at least 150 minutes (for moderate load) over 3–5 days per week, daily stretching, and strength training two or three times per week.[29,36,43] Risk management in post-discharge rehabilitation includes ultraviolet protection (prevention of GvHD of the skin) and infection control (e.g., herpes zoster, aspergillus pneumonia, viral cystitis). For patients on long-term steroid administration due to chronic GvHD, it is important to watch for complications of osteonecrosis, osteoporosis, and myopathy.

Complications in HSCT treatment

After HSCT, many patients experience a variety of complications. Typical examples include RRT, mucosal disorders, infection (bacterial, fungal), acute GvHD, cytomegalovirus, and hemorrhagic cystitis.[23,24] These complications can inhibit rehabilitation. Complications may lead to decreased activity and progressive loss of physical function (Fig. 4). Even in the presence of complications, exercise therapy should be continued as much as possible based on thorough assessment, and the patients should be fully informed.

Risk management for exercise therapy

Cytopenia

In addition to the general risk management of exercise therapy, another point that requires attention during HSCT rehabilitation is cytopenia. Since blood samples are usually drawn three times a week during HSCT hospitalization, it is advisable to confirm the blood test data before starting exercise therapy to ensure its safe implementation. In addition to cytopenia, the other following conditions should also be noted : coagulation abnormalities, deep vein thrombosis, pleural effusions/ascites, and edema.

Leukopenia

A low WBC count is not a specific contraindication to exercise therapy, but exercise therapy should be performed with careful attention to infection control. If the WBC count is $< 1{,}000/\mu L$ and the neutrophil count is $< 500/\mu L$, infection control measures should be thoroughly implemented.

Anemia

Hemoglobin levels are commonly used as an indicator of risk management related to anemia. A

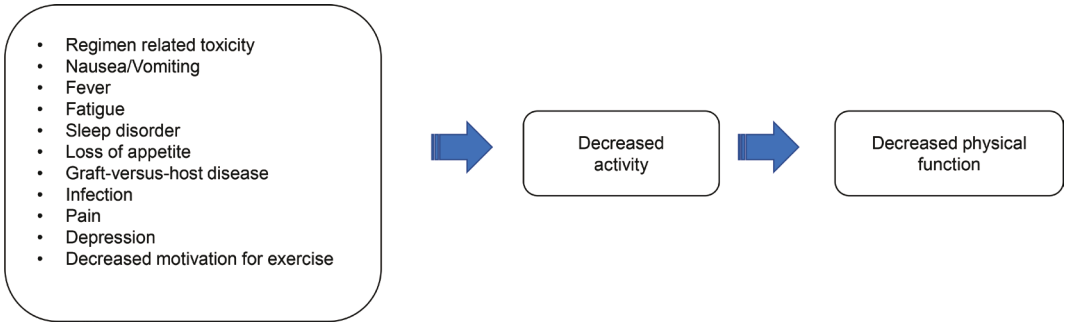

Fig. 4. Post-HSCT related factors affecting decreased physical function.

hemoglobin (Hb) level of ≤ 8 g/dL should preclude intensive exercise.[25] Even with an Hb < 8 g/dL, moderate supervised exercise is possible, with careful attention to clinical symptoms (anemia symptoms, fatigue, respiratory distress, and fall) under risk management for the patient.[25] If red blood cell transfusion is planned, implementing exercise therapy after the transfusion should be considered.

Thrombocytopenia

In cases where a patient with thrombocytopenia undergoes exercise therapy, special attention should be paid to the exercise intensity in order to prevent bleeding. If platelet transfusion is necessary, exercise should be performed after the transfusion.

Recent studies have reported that exercise therapy can be performed in HSCT patients with platelet levels of < 10,000/μL.[25,51] Mohammed *et al.*[25] reported that the following activities are indicators of feasibility when platelet counts are < 5,000/μL ; active assisted range of motion (AAROM) / active range of motion, essential activities of daily living (sitting at the edge of the bed or in the bed/chair), bed mobility (rolling, supine to sit on the edge of the bed), and therapeutic activity (active assistive movement for upper and lower extremities) in bed. AAROM and low-intensity activities such as sitting and standing are considered feasible even in patients with low platelet levels. Morishita *et al.*[51] also reviewed the prescription of exercises for patients with thrombocytopenia to prevent bleeding, and found that free weight training, but not exercise with resistance machines, was recommended. The results of this study indicate that resistance training is possible with a platelet count of ≥ 20,000/μL or higher. (Table 3).

When performing exercise therapy in patients with low platelet counts, careful supervised exercise should be performed with careful attention to falls, exercise intensity, and pressure on the skin.

Recovery of physical function after HSCT

Early recovery of physical function can be possible through the implementation of exercise therapy before and after transplantation.[31,33,52] Both physical function and QOL generally recover to pre-HSCT levels within one year, in cases with no or mild GvHD.[27,53] In some cases, the patients have returned to work and reached their pre-onset standard of living. Patients with high physical function may be able to return to work earlier.[27,54] On the other hand, GvHD and steroid administration are associated with factors that delay recovery of physical function after transplantation.[53] In long-term survivors, patients with higher physical function after discharge from the hospital also tend to have a better QOL.[55] Therefore, it is very important to explain to patients the necessity of maintaining physical activity after discharge from the hospital.

Conclusion

Various complications caused by HSCT treatment can cause HSCT patients to remain in hospital for extended periods of time. Rehabilitation performed with the goal of early discharge from the hospital and reintegration into society is extremely important.

On the other hand, a multidisciplinary approach is necessary to safely and effectively carry out exercise therapy. The HSCT team includes hematologists, physiatrists, dentists, psychiatrists, nurses, pharmacists, nutritionists, laboratory technicians, members of the radiology department and administrative department, physical therapist/occupational

Table 3. Recommended physical exercises and corresponding cutoff platelet values for patients with thrombocytopenia

Platelet Counts	Recommended Exercise
< 10,000/μL	Limit activity. Patient may require a platelet transfusion, before resuming exercise.
10,000-20,000/μL	Exercise gently, without resistance. Sitting or standing exercises, gentle stretching, and walking may be allowed.
20,000-50,000/μL	Resistance equipment such as weights, elastic tubing, or theraband may be used. The patients may be allowed to walk more briskly and practice step-ups or stairs.
50,000-80,000/μL	Activities such as stationary cycling and golfing are acceptable.
> 80,000/μL	The patient can perform vigorous resistance exercises and aerobic exercises such as biking or jogging. However, appropriate protective gear should be used, and precautions must be taken to avoid accidental injury.

Abbreviations ; AAROM ; active assisted range of motion. AROM ; active range of motion. ADL ; activities of daily living
Cited from reference 51.

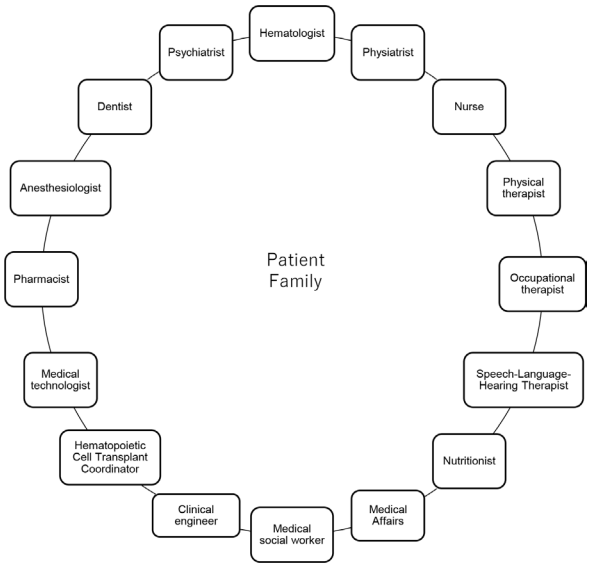

Fig. 5. Team approach.

therapist/speech-language-hearing therapist, and many others (Fig. 5). In addition to close daily information sharing among the staff, regular conferences should be continued to support HSCT patients. We believe that rehabilitation therapists should become a part of these teams and continue to support the patient toward their respective goals.

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Conflict of interest disclosure

The authors declare no conflict of interest.

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