The immediate impact of physical function and quality of life after hematopoietic stem cell transplantation

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Abstract

Purpose Although hematopoietic stem cell transplantation (HSCT) is a curative treatment for hematologic malignancies, HSCT survivors often experience declined physical function and quality of life (QoL). However, the physical function and QoL changes in acute post-transplant patients remain unclear. This study aimed to investigate the impact of HSCT on physical function.

Method This retrospective control study included 107 HSCT patients. Physical function was evaluated weekly from admission to discharge using the de Morton Mobility Index (DEMMI). Impaired physical function was defined as a baseline raw ordinal DEMMI score of < 17 and a decrease of ≥ 2 points. We collected the Visual Analog Scale (VAS), European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30), and Zung Self-rating Depression Scale (SDS) at enrollment and discharge.

Results Based on the DEMMI scores, 41 patients (38.3%) showed impaired physical function. A notable decrease in the DEMMI score was found in the first week after HSCT. In the EORTC QLQ-C30, physical function differed between the groups at admission and discharge. The good physical function group showed better cognitive function and social function. For the SDS, the impaired physical function group showed significantly higher depression at discharge.

Conclusion A third of the patients showed physical impairment during the acute transplant period. Patients with low physical function suffered more from depression and lower QoL. Evaluating patients’ pre-transplant physical function and early detection is needed as impaired physical function mainly occurs at 1 week post-transplant.

Keywords Hematopoietic stem cell transplantation · Physical function · Quality of life

Introduction

Hematopoietic stem cell transplantation (HSCT) is widely accepted as a standard treatment option for many hematologic diseases and select solid tumors, enabling high-dose chemotherapy and rebooting patients’ immune systems [1]. Various sources of HSCs are used for stem cell infusion in practice, including bone marrow, peripheral blood, cord blood, and even haploidentical donor HSCs [1, 2]. New conditioning regimens and developed techniques have reduced transplant-related mortality throughout the years [3]. Consequently, the accumulated number of HSCTs performed has been increasing globally with annual numbers in the 50,000 s [1], and reached approximately 1 million by December 2012 [4]. In order to be performed, HSCT requires a high level of infrastructure and resources to find a proper match. However, it is worthwhile as HSCT reduces mortality rates and cures thousands of patients with diseases previously recognized as non-curable every year [4].

Although there are clear benefits in mortality, HSCT changes the recipient’s whole-body system through high-dose chemotherapy and irradiation, resulting in many complications and discomfort. Graft versus host diseases (GVHD), toxicity of chemotherapy, and transplantation-related infections are serious consequences of HSCT and are known to contribute to treatment-related mortality...
One of the most common complications is mucositis, which can involve both the oropharynx and intestine and hampers patients from receiving proper nutrition [1]. During HSCT, the recipients are required to remain in an isolated room. Aside from these somatic effects, HSCT is also associated with psychological and psychosocial side effects and recipients encounter functional and quality of life (QoL) decline after HSCT [6, 7].

Physical function (PF) can be defined as the ability to perform basic actions that are essential for maintaining independence and carrying out more complex activities. PF is essential for performing activities of daily living (ADL) and instrumental ADLs [8]. People with low PF suffer from decreased QoL and an increased risk of depression and disability [9]. Impaired PF leads to decreased mobility, which is associated with various medical conditions such as osteoporosis [10], pressure ulcers [11], and increased fall risk [12] and contributes to an increased health care burden [9]. Thus, it is necessary to assess PF limitations and intervene at an optimal time to maintain PF. Physical exercise interventions have proven effective in improving or preserving PF in various population groups including HSCT recipients [13–16]. Many researchers have assessed PF using self-reported questionnaires or measuring specific exams such as grip strength, 6-min walking test, Timed-Up-and-Go test, and Karnofsky Performance Status (KPS) [6, 7, 17].

PF decline after HSCT is known to occur during inpatient stay, which means the acute phase of post-transplant and patients recover their pre-transplant status within 12 months after HSCT [6, 18]. The importance of PF after HSCT suggests that patient-reported PF early post-HSCT has prognostic value in survival probability [19]. Physical rehabilitation is proposed as an effective tool to relieve HSCT-related burden, and exercise during hospitalization reduces fatigue and leads to higher QoL in HSCT recipients [20]. Even more, rehabilitation before HSCT has shown its effectiveness and feasibility in alleviating fatigue and improving physical function [21–24].

Although many studies have focused on changes in functioning and QoL after HSCT, most of them are long-term follow-up studies and outpatient programs. The aim of this study was to investigate the impact of HSCT on PF using the de Morton Mobility Index (DEMMI) and QoL in the acute phase of post-HSCT during hospitalization. We also aimed to identify which domains of QoL are related to PF after HSCT to determine the right time for intervention.

Method

Hematopoietic stem cell transplantation

The patients underwent HSCT with the purpose to cure their disease and HSCT was performed using the conventional method. Hematologists carefully eradicated the patient’s HSCs using various conditioning regimens.

Allogeneic stem cells were mostly collected by peripheral mobilization from donors after G-CSF administration. However, a small proportion of patients received cord blood stem cells. Infusion of the collected allogeneic and autologous HSCs was performed in aseptic rooms with working HEPA-filters. After confirming that the transplanted bone marrow engrafted successfully, the patients were discharged home and not followed by the Department of Rehabilitation Medicine unless there were special concerns.

Design and participants

This study was a retrospective control study involving hematologic cancer patients who were scheduled to undergo HSCT at one hospital located in South Korea, between August 2016 and December 2020.

The inclusion criteria were as follows: (1) age ≥ 18 years, (2) planning to receive HSCT whether autologous or allogeneic, and (3) able to read and answer self-reporting questionnaires at the time of admission and discharge. We excluded patients who (1) had severe underlying medical conditions that could impair their PF such as shock, severe infection, cardiovascular diseases, and severe musculoskeletal problems and (2) who could not complete the physical therapist’s command for DEMMI score evaluation.

Eligible 182 patients were enrolled, but 26 patients were discontinued participation because severe medical conditions such as shock, uncontrolled infection developed during inpatient period. Total 49 patients were dropped out because they could not complete self-reporting questionnaires either at the time of admission or discharge or failed to measure the DEMMI scores more than 2 weeks during pre-transplant and post-transplant 3 weeks (Fig. 1). Total 107 patients participated in this study. This study was approved by the Institutional Review Board of the Seoul National University Hospital. Informed consent was obtained from all patients.

Monitoring of physical function via the DEMMI scores

Each patient’s PF was assessed weekly until discharge using the DEMMI score by trained physical therapists. The baseline score was collected before HSCT or within the first week of HSCT. In addition, rehabilitation treatment was provided for patients if a decrease in the DEMMI score was detected or if the initial DEMMI score was <70 (ordinal raw score 17) with the patient’s consent. Rehabilitation treatment sessions were given to improve individual patients’ PF; thus, muscle strengthening exercises, sitting and standing balance, and gait training were included. Rehabilitation treatment sessions were provided in the gym or at the bedside for 30 min, 3 times a week.
Outcome variables

We reviewed the medical records of the patients and recorded the hematopoietic cancer type, HSCT type, and body weight. Laboratory data, including complete blood count, absolute neutrophil count, aspartate aminotransferase, alanine aminotransferase, blood urea nitrogen, serum creatinine, and albumin, were also collected at the time of admission, beginning of HSCT, and discharge.

The DEMMI score was recorded as an ordinal raw score ranging from 0 to 19 points and converted to an interval-level score ranging from 0 to 100 through a conversion table.

Group categorization

Patients were categorized into two groups according to their DEMMI scores. Impaired PF was defined as a decrease in two or more points of the raw ordinal DEMMI scores or the measured raw ordinal DEMMI score < 17 at baseline. Patients who met these criteria at least once were classified into the impaired PF group. Those who did not meet these criteria were classified into the good PF group. Once patients belonged to either one group, the patients remained in the group throughout the study.

Self-reported QoL outcome variables

We obtained outcome variables to assess QoL of the patients using the Visual Analog Scale (VAS), European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30), and Zung Self-rating Depression Scale (SDS). Patients were asked to complete the questionnaires at the time of admission and discharge.

We used the validated Korean version of the EORTC QLQ-C30, which is composed of five functional scales including physical, role, emotional, cognitive, and social functioning. Functional scales ranged from 0 to 100, with higher scores indicating higher functioning abilities. The SDS validated in Korean was used to evaluate the severity of depression in the patients, and a higher SDS score indicates more severe depression in the patient.

Statistical analysis

Clinical demographic data of the patients were analyzed using an independent t-test for age. The chi-squared tests were used to compare the expected frequencies for gender and type of HSCT between groups. Type of cancer was analyzed using Fisher’s exact tests to compare the expected frequencies between groups.

We analyzed the DEMMI scores according to weeks (time) from pre-transplant to post-transplant 3 weeks, between the groups using repeated measures analysis of variance (RM-ANOVA). The paired t-test was used in post hoc analysis to compare the DEMMI score change within the group. SPSS version 26.0 (SPSS, Inc., Chicago, IL, USA) was used for all statistical analyses. The p-value threshold for statistical significance was set at p < 0.05.

Results

Patient characteristics

The mean age of all patients was 50.84 ± 13.76 years, and 63.5% of the patients were men (Table 1). The most
common cancer type was lymphoma \((n = 27)\), followed by acute myeloid leukemia \((n = 22)\). Five types of cancer have \(\geq 10\) patients in our cohort. Of the 107 patients, 38 (35.5\%) and 69 patients (64.5\%) underwent autologous HSCT and allogeneic HSCT, respectively. During hospitalization, 14 patients (13.08\%) participated in rehabilitation treatment sessions. The mean hospitalization period was \(39 \pm 34.61\) days and median length of stay was 32 days. One patient was diagnosed as acute GVHD of liver and GI tract 35 days after HSCT.

**Physical function measured by DEMMI scores after HSCT**

The initial baseline DEMMI score of all patients \((n = 107)\) was \(89.83 \pm 14.37\). The good PF group \((n = 66)\) showed a significantly higher score than the impaired PF group \((n = 41)\) at baseline \((93.71 \pm 8.81\) vs. \(83.59 \pm 18.88\)). Also, we observed a marked decrease in the DEMMI score measured in the first week after HSCT in the impaired PF group \((77.74 \pm 17.82)\). However, in the good PF group, no DEMMI score drop was detected during hospitalization. Although we found a small increase in DEMMI scores in the good PF group throughout the hospitalization period, the increase was not statistically significant. The reduction in DEMMI scores in the first week in the impaired PF group could not be restored until discharge. The measured DEMMI scores at the first, second, and third weeks remained similar, with an insignificant difference. The DEMMI scores of the two groups during hospitalization are shown in Fig. 2. The impaired PF group demonstrated significantly lower DEMMI scores than the good PF group at baseline and at the first, second, and third weeks (Fig. 3).

**Self-reported QoL outcome variables between groups**

We compared the self-reported QoL outcome variables between the good and impaired PF groups (Table 2). We could not see any significant differences in VAS scores between the groups at the time of admission and discharge.

### Table 1 Demographics and clinical characteristics

|                      | Good PF (mean ± SD) | Impaired PF (mean ± SD) | \(p\)-value |
|----------------------|---------------------|-------------------------|-------------|
| Subjects \((n)\)     | 66                  | 41                      |             |
| Age (year) (mean ± SD) | 52.44 ± 13.16      | 48.50 ± 14.51           | 0.151       |
| Gender               |                     |                         | 0.207       |
| Female               | 21                  | 18                      |             |
| Male                 | 45                  | 23                      |             |
| Type of cancer \((n)\) |                     |                         | 0.079       |
| Lymphoma             | 16                  | 11                      |             |
| Acute myeloid leukemia | 16                | 6                       |             |
| Multiple myeloma     | 12                  | 7                       |             |
| Myelodysplastic syndrome | 15             | 4                       |             |
| Acute lymphoblastic leukemia | 3  | 7                      |             |
| Aplastic anemia      | 2                   | 1                       |             |
| Chronic myeloid leukemia | 1                | 2                       |             |
| Acute biphenotypic leukemia | 0 | 2                      |             |
| Rhabdomyosarcoma     | 1                   | 0                       |             |
| Yolk sac tumor or testis | 0              | 1                       |             |
| Type of HSCT \((n)\) |                     |                         | 0.517       |
| Autograft            | 25                  | 13                      |             |
| Allograft            | 41                  | 28                      |             |
| Rehabilitation \((n)\) | 0                  | 14                      | 0           |

PF, physical function; SD, standard deviation; HSCT, hematopoietic stem cell transplantation

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**Fig. 2** The de Morton Mobility Index (DEMMI) scores change after HSCT. PF, physical function; HSCT, hematopoietic stem cell transplantation. The impaired physical function group scores significantly lower DEMMI after the first week of HSCT and does not recover until the third week \((p < 0.05)\). Statics performed by paired \(t\)-test, comparing the DEMMI scores at each week versus baseline. Asterisks indicate \(p < 0.05\).
In the EORTC QLQ-C30 functioning scale, there were some notable differences between the groups. PF showed significant differences both at the time of admission and at discharge. In cognitive functioning, the good PF group performed better than the impaired PF group only at admission. The impaired PF group scored significantly lower than the good PF group only at discharge in social functioning. The impaired PF group showed significantly higher depression at discharge than the good PF group.

**Laboratory findings between groups**

We compared the collected laboratory data between groups, and there was no significant difference at admission, the start date of HSCT, and discharge.

**Discussion**

Our study showed that impaired PF in the acute post-transplant period of HSCT during hospitalization occurs in over a third of the recipients, mainly in the first week after HSCT. In our previous study with 41 patients, 24.40% of patients experienced a decline in PF after HSCT [25]. Few studies have investigated PF changes after HSCT during the inpatient period. Hacker et al. [26] found that physical activity decreased and fatigue increased on the fifth day after HSCT compared to before HSCT. In line with these previous studies, our findings suggest that HSCT impairs the recipient’s PF within the first week post-transplant; thus, PF decline can be detected early in the hospitalization period. Relatively long-term follow-up studies also found that PF dropped to the lowest level at the time of discharge and recovered over several months [18, 27, 28]. Our study focused on the acute change in PF during the hospitalization period after HSCT, while other studies assessed PF mostly at the time of discharge, at 4–6 weeks, 2 months, 3 months, and 1 year.

One possible explanation for the decline in PF in the acute post-transplant period is physical inactivity or bed rest during HSCT. A preparative regimen of high-dose...
chemotherapy and sometimes total-body irradiation precedes HSCT to destroy the recipient’s immune system. As a result, the recipient becomes immunocompromised and prone to bleeding due to severe leukopenia and thrombocytopenia. Thus, the patient is required to stay in an isolated single bed with a working HEPA filter. Kortebein et al. reported that 10 days of bed rest in healthy older people (mean age: 67 ± 5 years) resulted in marked loss of lean tissue from the lower extremity and showed significantly lower strength of the lower extremities and maximal aerobic capacity compared to baseline [29]. Although our patients’ mean age was much younger (50.84 ± 13.76 years), it is noteworthy that 10 days of physical inactivity could cause loss of leg muscle mass and strength and aerobic capacity, and this could provide a plausible explanation for the decline in PF at the first week after HSCT in our study.

Our research revealed several differences in self-reported QoL variables between low PF and good PF. The patients evaluated themselves using the EORTC QLQ-C30 scale at admission and discharge. Our study demonstrated that better cognitive function at baseline was associated with good PF, and better PF was associated with less depression at discharge. Numerous studies have shown similar findings that subjective cognitive impairment is related to QoL difficulties and psychological symptoms such as depression in HSCT recipients in the long term. A study conducted by Booth-Jones et al. reported that poorer cognitive function was associated with poorer PF and more severe depression at 6 months after HSCT [30]. Our findings vary from these previous reports in that they found a link between low cognitive function, physical impairment, and QoL difficulty after HSCT. Our findings suggest that cognitive impairment may be a predictive factor for the decline in PF decline after HSCT, and there is evidence that cognitive function decline negatively affects PF in the elderly. Auyeung et al. reported that cognitive function decline in dementia might contribute to PF impairment independent of muscle mass [31]. In our cohort, a decline in social function was detected in the physically impaired group at discharge. Social functioning is an essential skill for living with others outside the hospital and returning to work. Person et al. summarized the importance of returning to work for HSCT survivors and claimed that their return to work may improve the QoL of the patients [32]. As low social functioning could further hinder the recovery of HSCT survivors, physicians should carefully consider social function as well as PF.

The importance of maintaining PF after HSCT can be suggested in that physical function is associated with other functioning and depression. Also, Wood WA et al. demonstrated decreases in physical component of patient-reported outcomes 100 days after HSCT were connected with higher overall mortality and treatment-related mortality [18]. Physical rehabilitation interventions in HSCT patients have shown its potential to alleviate fatigue and enhance QoL [19]. Our study revealed above a third of HSCT survivors encounter decreased PF as early as 1 week post-transplant. Impaired PF in acute post-HSCT period should always be of interest to physicians because physical rehabilitation may help recover or retain PF in an effective and timely manner. In addition, it would be helpful to let patients’ caregivers and physiotherapists be aware of the findings of our study. Knowing the importance and downward trend of PF in acute post-HSCT would help caregivers to notice the recipients’ changes and lead patients to have more physical activity.

In our study, we provided the rehabilitation treatment sessions to 14 patients in the impaired PF group. But we failed to show the effect of given programs on PF compared to no treatment group. This might be explained that we were not able to intervene right time and the hospitalization period was too short to reflect changes. The pre-habilitation programs started to draw attention and several studies have shown the effectiveness on lower fatigue and higher physical function and QoL [16, 24]. The rehabilitation before HSCT can be helpful because it can restore physical reserve which gives strength to patients to get over with massive changes HSCT would bring. Further studies including rehabilitation interventions on HSCT patients should be long enough in time to get meaningful results.

Laboratory findings, including serum albumin, total protein, and hemoglobin, did not show any differences in relation to PF. Because mucositis and GVHD of the GI tract might have negative effects on nutrition absorption, the nutritional status of HSCT recipients has been of interest to researchers. Ferreira et al. compared laboratory data before and after HSCT and reported a significant decrease in serum albumin levels [33]. Our research analyzed the laboratory changes within 1 month; therefore, it is possible that the follow-up period was too short to reflect systematic changes according to PF.

The main strength of this study was that we assessed objective PF changes via the DEMMI scores by rehabilitation therapists. The DEMMI score is a widely validated measuring system and consists of 15 hierarchical mobility items, including three beds, three chairs, four static balances, two walking, and three dynamic balance items [34]. Many previous studies evaluated PF using the Eastern Cooperative Oncology Group performance, the Karnofsky Performance Scale, and the 6-min walk test. These assessments have shortcomings in that they cannot point out the aspects that are lacking in the patients’ PF and cannot provide triage to rehabilitation, so further rehabilitation therapy targets are vague [8]. Through the DEMMI scoring system, a proper rehabilitation program can be provided according to individual needs and weak points. There is no single standardized assessment tool for PF in HSCT recipients. Further research should validate the proper PF assessment tool and check the efficiency of physical rehabilitation in HSCT survivors.
This study had several limitations. First, this was a retrospective control study conducted at a single center. Our study enrolled over 100 patients. To our knowledge, this cohort study is the largest among the studies that assessed PF repeatedly during the inpatient period. However, our study sample size was insufficient for multivariate analyses. Lastly, there are missing data of the DEMMI scores because we could not assess patients if their medical condition deteriorated after HSCT; for example, if the patients were transferred from the ward to the intensive care unit. We excluded patients if there were two or more missing exams; thus, our study had weaker generalizability. Future research with multi-centered large prospective study design might show general physical function changes after HSCT and identify the factors that make HSCT patients more prone to physical function decline.

Conclusion

We observed that more than one-third of patients showed physical impairment after HSCT during the acute post-transplant period, and PF decline was associated with more severe depression and lower QoL. Evaluating the recipient’s pre-transplant PF and early detection of any decline in PF after HSCT is needed because a low baseline PF cannot be restored and impaired PF mainly occurs at 1 week post-transplant. Appropriate physical rehabilitation interventions may help prevent further decline in PF. Physicians should keep an eye on recipients’ physical function after HSCT.

Author contribution Dr YeJi Lee, Prof InHo Kim, and Prof Seo planned this study and wrote the main manuscript text. Prof YounIl Goh, Prof DongYeop Shin, and Prof JunShik Hong wrote parts of method and discussion about hematopoietic stem cell transplantation. Dr. Chang Won Lee analyzed data and prepared figures. All authors reviewed the manuscript.

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Data availability The data that support the findings of this study are available from the corresponding author upon a reasonable request.

Code availability Not relevant.

Declarations

Ethics approval Approval was obtained from the ethics committee of the Seoul National University Hospital. The procedures used in this study adhere to the tenets of the Declaration of Helsinki.

Consent to participate Informed consent was obtained from all individual participants included in the study.

Consent for publication Not relevant.

Conflict of interest The authors declare no competing interests.

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