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ORIGINAL ARTICLE

Pre-transplant Rehabilitation to Decrease the Post-transplant Length of Stay for Hematological Malignancy Patients Undergoing Allo-HSCT

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Objectives: Pre-transplant rehabilitation for hematological malignancy patients undergoing allogeneic hematopoietic stem cell transplantation (allo-HSCT) helps improve physical capacity. However, its benefit with respect to post-transplant hospital length of stay (LOS) is unclear. Consequently, the aim of this study was to investigate the effect of pre-transplant rehabilitation on post-transplant LOS for hematological malignancy patients undergoing allo-HSCT. **Methods:** Data on patients diagnosed between April 2014 and March 2017 were collected from the Japanese Diagnosis Procedure Combination database. The patients were identified using the ICD-10 codes C81–85, C90–94, C96, and D46. Multilevel linear regression analyses were conducted to identify the effects of pre-transplant rehabilitation on post-transplant LOS (log transformed). **Results:** In total, 3614 patients were included in the study. Pre-transplant rehabilitation was associated with a significant reduction in post-transplant hospital LOS (β=–0.134, P<0.001). **Conclusions:** Pre-transplant rehabilitation may be an effective strategy for shortening the post-transplant hospital LOS in hematological malignancy patients undergoing allo-HSCT. Consequently, it may be necessary to consider starting rehabilitation before transplantation.

Key Words: allogeneic hematopoietic stem cell transplantation; hematological malignancy; length of stay; pre-transplant rehabilitation

INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a highly invasive treatment that can lead to a decline in physical capacity.[1,2] Such a decrease in physical capacity during hospitalization may prolong the patient's length of stay (LOS) and, consequently, its prevention is important. Exercise-based rehabilitation is safe for HSCT patients[3] and is known to help improve physical capacity. Several meta-analyses have shown that exercise intervention in patients undergoing HSCT has positive effects on cardiorespiratory fitness[4]; upper muscle strength[4]; lower muscle strength[4,5]; fatigue[4–6]; quality of life (QOL)[4–6]; and physical, emotional, and cognitive functioning.[4]

Rehabilitation for hospitalized transplant patients is divided into two parts: pre-transplant and post-transplant rehabilitation. Pre-transplant rehabilitation is important because HSCT patients have reduced physical capacity

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resulting from both the effects of the disease itself and the treatments delivered before HSCT.[7,8] Better physical capacity before transplantation is associated with better outcomes after transplantation.[9] Further, studies have indicated the effectiveness of pre-transplantation exercise for improving physical capacity after transplantation.[2,10–14] Liang et al. reported a sub-analysis of a meta-analysis indicating that exercise had a favorable effect on physical capacity, fatigue, and QOL when started before HSCT.[5]

Pre-transplant rehabilitation may prevent the deterioration of physical capacity and contribute to a shorter hospital stay. However, the relationship between pre-transplant rehabilitation and post-transplant hospital LOS remains unclear. Consequently, the purpose of this study was to investigate, using real-world data from Japanese acute care hospitals, the impact of pre-transplant rehabilitation on post-transplant hospital LOS in patients with hematologic malignancy undergoing allo-HSCT.

MATERIALS AND METHODS

Study Design and Patients

This was a retrospective observational study using the Japanese Diagnosis Procedure Combination (DPC) database. The subjects were patients with hematological malignancy who underwent allo-HSCT (n=8340). The patients were identified and classified using the ICD-10 codes C81 (Hodgkin lymphoma), C82–C85 and C96 (non-Hodgkin lymphoma), C90 (multiple myeloma), C91 (lymphoid leukemia), C92–94 (myeloid leukemia), and D46 (myelodysplastic syndrome) in reference to a previous study.[15] The exclusion criteria were (1) age younger than 18 years, (2) not independent in activities of daily living (ADLs) at the time of admission [Barthel index (BI) score <100], (3) hospitalization for longer than 30 days between hospitalization and allo-HSCT, (4) multiple transplants during hospitalization or unknown stem cell source, (5) death during hospitalization, and (6) missing data.

This study was approved by the institutional review board of the University of Occupational and Environmental Health, Japan (R2-007), which deemed that written informed consent from participants was unnecessary.

Data Source

The DPC is a case-mix patient classification system launched in 2002 by the Ministry of Health, Labour, and Welfare of Japan. It contains information on lump-sum per-diem payment for hospitalized patients and other data including date of birth, hospitalization, discharge, sex, name of main injury or illness (ICD-10 code), complications, comorbidity (Charlson comorbidity index, CCI), surgical procedures, other major measures, and patient status at the time of discharge.[16,17] The database stores data for approximately 7 million patients annually from more than 1000 participating hospitals. Furthermore, the database covers more than 50% of all acute-care inpatients and approximately 90% of all tertiary-care emergency hospitals in Japan.[17] In the current study, we used case data for patients discharged between April 2014 and March 2017.

Analysis of Variables

We selected patient-level factors and hospital-level factors that could potentially affect post-transplant hospital LOS. Patient-level factors were age, sex, body mass index (BMI), stem cell source, underlying disease, CCI, secondary disease [graft-versus-host disease (GVHD: T860, T868), cytomegalovirus infection (B259), bacterial infection (A499), candidiasis (B37)], pressure ulcer (L89), performance of pre-transplant rehabilitation, and frequency of rehabilitation. In this study, pre-transplant rehabilitation was defined as the execution of at least one rehabilitation session prior to transplantation. The hospital-level factor was the status as a university or non-university hospital.

Statistical Analysis

Unpaired *t*-tests and chi-squared tests were used to compare the characteristics of the pre-transplant rehabilitation [PTR(+)] group and the no-pre-transplant rehabilitation [PTR(–)] group. Multilevel linear regression analyses (univariate/multivariate) were conducted to identify the effects of pre-transplant rehabilitation on post-transplant hospital LOS; this approach was used because it is possible that the hospitals to which patients were admitted influenced both the treatment during hospitalization and the post-transplant LOS. Multilevel analysis was used to simultaneously analyze the impact of hospital factors and patient factors and to examine the impact of hospital characteristics on patients.[18] The natural-logarithm-transformed post-transplant hospital LOS was used as the outcome variable; this transformation was applied because LOS data exhibited a positive distortion in its distribution. The explanatory variables used were age, sex, BMI, stem cell source, diagnosis, CCI, secondary disease, university hospital status, pre-transplant rehabilitation (binary variable), and rehabilitation frequency. The absence of strong correlations (>0.8) between explanatory variables was confirmed beforehand by correlation analysis. All statistical analyses were performed using STATA release 16

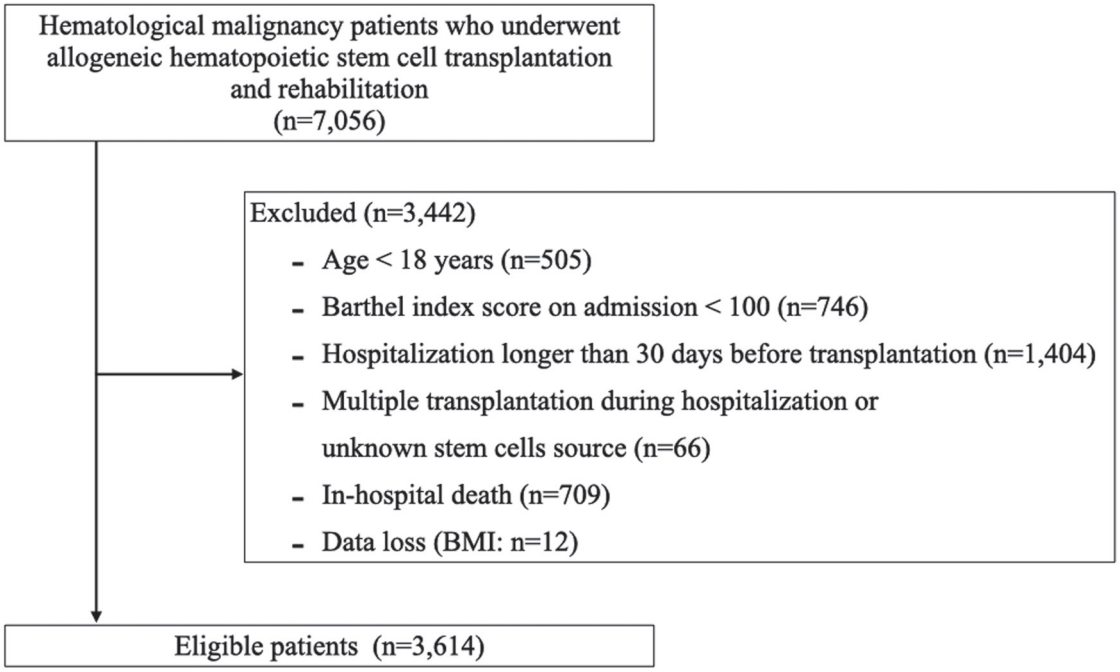

Fig. 1. Patient selection flowchart. In total, 3614 patients with hematological malignancy undergoing allogeneic hematopoietic stem cell transplantation were included in the study.

(Stata, College Station, TX, USA). A P value of <0.05 was considered statistically significant.

RESULTS

In total, 3614 patients with hematological malignancy who underwent allo-HSCT were included in this study (**Fig. 1**). **Table 1** shows the patient characteristics. Overall, 2728 patients underwent pre-transplant rehabilitation. The stem cell source (P=0.038) and the percentage of patients with GVHD complications (P=0.030) were significantly different between the PTR(+) group and the PTR(–) group. The interval between HSCT and the start of post-transplant rehabilitation, the duration of rehabilitation, and the frequency of rehabilitation were also significantly different between the two groups (all P<0.001).

Table 2 shows the comparison of patient outcomes between the two groups. Post-transplant hospital LOS was significantly shorter in the PTR(+) group than that in the PTR(–) group (mean: 74.2 vs. 90.2 days, P<0.001). The overall LOS was also significantly shorter in the PTR(+) group (mean: 89.9 vs. 104.2 days, P<0.001). Furthermore, the BI score at discharge was not significantly different between the two groups (mean: 93.8 vs. 93.1, P=0.430). The overall cost of hospitalization was lower in the PTR(+) group (mean: $84,594 vs. $95,285; P<0.001).

Table 3 shows the results of multilevel linear regression analysis with the log-transformed post-transplant LOS as the explained variable. Pre-transplant rehabilitation was associated with a significant reduction in post-transplant LOS (β=–0.134, P<0.001). Peripheral blood transplantation was also significantly associated with a shorter post-transplant LOS (β=–0.072, P<0.001). In contrast, cord blood transplantation (β=0.144, P<0.001), lymphoid leukemia (β=0.034, P=0.038), Hodgkin lymphoma (β=0.247, P=0.002), CCI ≥2 (β=0.078, P=0.002), GVHD complications (β=0.091, P<0.001), cytomegalovirus infection (β=0.127, P<0.001), and frequency of rehabilitation (β=0.138, P=0.006) were significantly associated with a longer post-transplant LOS.

DISCUSSION

The effect of pre-transplant rehabilitation on the post-transplant hospital LOS in hematologic malignancy patients undergoing allo-HSCT is not clear. Our results show that pre-transplant rehabilitation has the potential to shorten the hospital LOS for hematological malignancy patients who undergo allo-HSCT. The mean duration of pre-transplant rehabilitation in this study was 10.8 days, which is consistent with previous studies in Japan that initiated pre-transplant re-

Table 1. Patient characteristics

	Total		Pre-transplant rehabilitation				
			Yes		No		
	n	(%)	n	(%)	n	(%)	P-value
Number of patients	3614		2728		886		
Age (years), mean (SD)	49.3	(13.7)	49.3	(13.7)	49.6	(13.8)	0.536
Sex							0.412
Female	1507	(42)	1148	(42)	359	(41)	
Male	2107	(58)	1580	(58)	527	(59)	
Body mass index (kg/m^2)							0.934
<18.5	585	(16)	445	(16)	140	(16)	
18.5 to <25.0	2490	(69)	1876	(69)	614	(69)	
≥25.0	539	(15)	407	(15)	132	(15)	
Stem cell source							0.038
Bone marrow	1532	(42)	1131	(41)	401	(45)	
Peripheral blood	1085	(30)	848	(31)	237	(27)	
Cord blood	997	(28)	749	(27)	248	(28)	
Underlying disease							0.105
Myeloid leukemia	1656	(46)	1252	(46)	404	(46)	
Lymphoid leukemia	973	(27)	715	(26)	258	(29)	
Myelodysplastic syndrome	560	(16)	442	(16)	118	(13)	
Non-Hodgkin lymphoma	363	(10)	278	(10)	85	(10)	
Multiple myeloma	36	(1)	23	(1)	13	(2)	
Hodgkin lymphoma	26	(1)	18	(1)	8	(1)	
Charlson comorbidity index							0.319
0	2835	(78)	2155	(79)	680	(77)	
1	477	(13)	354	(13)	123	(14)	
≥2	302	(8)	219	(8)	83	(19)	
Secondary disease							
Graft-versus-host disease	490	(11)	277	(10)	113	(13)	0.030
Cytomegalovirus infection	193	(5)	145	(5)	48	(5)	0.906
Bacterial infection	12	(0)	9	(0)	3	(0)	0.969
Candidiasis	70	(2)	53	(2)	17	(2)	0.964
Rehabilitation, mean (SD)							
Interval between start of pre-transplant rehabilitation and HSCT (days)			10.8	(5.2)			
Interval between HSCT and start of post-transplant rehabilitation (days)	11.8	(20.9)	5.2	(10.1)	31.8	(30.3)	<0.001
Duration of rehabilitation (days)	35.9	(24.5)	38.3	(24.2)	28.2	(23.9)	<0.001
Frequency of rehabilitation (days/length of stay)	0.39	(0.2)	0.43	(0.2)	0.26	(0.1)	<0.001
University hospital (yes)	1750	(49)	1376	(50)	374	(42)	<0.001

SD, standard deviation.

habilitation 1–4 weeks before transplantation.[19–21] However, this period is longer than that reported in previous studies in some other countries (mean: 6–7 days).[2,10] Such differences between Japan and other countries could be influenced by differences in the respective medical systems.

Hematological malignancy patients who undergo allo-HSCT have impaired physical capacity before transplantation.[7,8] Although the current study included only patients

Table 2. Comparison of outcomes between the pre-transplant rehabilitation and no-pre-transplant rehabilitation groups

	Pre-transplant rehabilitation						
	Yes			No			
	Mean	SD	95% CI	Mean	SD	95% CI	P- value
Post-transplant length of stay (days)	74.2	39.5	72.7–75.7	90.2	52.3	86.7–93.6	<0.001
Total length of stay (days)	89.9	40.5	88.3–91.4	104.2	53.3	100.7–107.7	<0.001
Barthel index score at discharge	93.8	22.3	92.9–94.6	93.1	22.2	91.6–94.6	0.430
Total cost of hospitalization (USD)	84,594	43,260	82,970–86,218	95,285	54,873	91,667–98,903	<0.001

CI, confidence interval.

Table 3. Multilevel linear regression analysis of factors influencing post-transplant length of hospital stay (log transformed)

	Univariate analysis			Multivariate analysis		
	β	SE	P-value	β	SE	P-value
Intercept				4.251	0.042	<0.001
Age (years)	0.001	0.001	0.023	<0.001	0.001	0.378
Male sex	–0.023	0.014	0.100	–0.016	0.014	0.238
Body mass index (kg/m^2)						
<18.5	0.026	0.019	0.171	0.007	0.019	0.701
18.5 to <25.0	Reference					
≥25.0	–0.013	0.020	0.492	–0.001	0.019	0.981
Stem cell source						
Bone marrow	Reference					
Peripheral blood	–0.081	0.017	<0.001	–0.072	0.017	<0.001
Cord blood	0.115	0.017	<0.001	0.144	0.017	<0.001
Underlying disease						
Myeloid leukemia	Reference					
Lymphoid leukemia	0.032	0.017	0.006	0.034	0.016	0.038
Myelodysplastic syndrome	0.024	0.020	0.238	0.025	0.020	0.217
Non-Hodgkin lymphoma	0.002	0.024	0.920	0.021	0.023	0.375
Multiple myeloma	0.132	0.070	0.059	0.124	0.068	0.066
Hodgkin lymphoma	0.227	0.082	0.015	0.247	0.079	0.002
Charlson comorbidity index						
0	Reference					
1	0.005	0.021	0.825	0.006	0.021	0.787
≥2	0.099	0.026	<0.001	0.078	0.026	0.002
Secondary disease						
Graft-versus-host disease	0.110	0.024	<0.001	0.091	0.024	<0.001
Cytomegalovirus infection	0.162	0.032	<0.001	0.127	0.032	<0.001
Bacterial infection	–0.135	0.119	0.259	–0.162	0.116	0.161
Candidiasis	–0.061	0.050	0.230	–0.081	0.049	0.098
Rehabilitation						
Pre-transplant rehabilitation (yes)	–0.118	0.019	<0.001	–0.134	0.020	<0.001
Frequency of rehabilitation	0.029	0.048	0.544	0.138	0.050	0.006
University hospital (yes)	0.027	0.037	0.462	0.049	0.037	0.175

SE, standard error.

who had complete independence in ADLs, it is assumed that many subjects likely had reduced physical capacity. Moreover, pre-transplant rehabilitation might help patients understand the significance and necessity of rehabilitation even before transplantation has taken place. Pre-transplant rehabilitation could have contributed to shortening the post-transplant LOS by reducing the decline in pre-transplant physical capacity and by supporting the early start of post-transplant rehabilitation. Moreover, a shorter post-transplant hospital LOS probably contributed to a shorter total hospital LOS, which in turn likely reduced the total cost of hospitalization.

Some studies have shown that preoperative rehabilitation reduces hospital LOS in lung cancer patients.[22–27] In the current study, we clarified the benefit of preoperative rehabilitation in patients with hematologic malignancy scheduled to undergo allo-HSCT. Despite the benefits of pre-transplant rehabilitation, the number of days available for such rehabilitation during hospitalization for HSCT is limited. Therefore, we considered it desirable to start pre-transplant rehabilitation in an outpatient setting or as a home program before hospitalization for HSCT. A previous study showed that 4–6 weeks pre-transplant rehabilitation before hospitalization for HSCT helped reduce the hospital LOS for HSCT without adverse events.[13]

In addition to pre-transplant rehabilitation, the transplant source, higher CCI, and complications (GVHD and cytomegalovirus infection) also affected post-transplant LOS. The difference in the post-transplant course for the different transplant sources might also have influenced the post-transplant LOS. Therefore, it will be necessary to verify each transplant source in future studies. A higher CCI is known to be a poor prognostic factor[28] and was also found to be a predictor of prolonged post-transplant hospital LOS in the current study. Both GVHD and cytomegalovirus infection are known from previous studies to be associated with longer hospital stays,[29,30] and the results of the current study are consistent with those results. It is a useful finding that pre-transplant rehabilitation was associated with shorter post-transplant LOS, even when adjusted for post-transplant complications.

The current results suggest that pre-transplant rehabilitation contributes to shorter post-transplant hospital LOS regardless of whether the hospital is a university hospital. However, the implementation of pre-transplant rehabilitation differed between academic and non-academic hospitals. This may reflect differences in facilities, size of workforce, hospital case volume, or the background of the patients undergoing HSCT. In the future, it will be necessary to examine the reasons for the differences in the implementation of pre-transplant rehabilitation at different facilities.

This study has some limitations. First, the type of pre-transplant rehabilitation implemented was not specified, and therefore the most appropriate rehabilitation strategy could not be established. Second, the type and duration of pre-transplant treatment prior to hospitalization were also unclear. The longer that a course of treatment not including rehabilitation continues, the more likely it is that a decline in physical capacity will occur, which could affect the LOS. However, we included only subjects who were fully independent in ADLs, thereby minimizing this impact on the study findings. Third, the patient's physical condition before allo-HSCT was unknown. Although pre-transplant rehabilitation is generally provided to patients in a good physical condition, it may have also been implemented in patients with poor physical condition such that rehabilitation needed to be started before transplantation. Consequently, our results should be interpreted with caution. Adjusting for subjective symptoms (e.g., fatigue) and the results of biochemical examinations (e.g., red blood cell, hemoglobin, and albumin levels) may solve this problem. However, the DPC database does not include these data, which is another limitation of this study. Finally, limited data were collected because of the retrospective nature of the study. Therefore, we were not able to adjust for confounding factors associated with longer LOS such as psychiatric morbidity,[31] oral mucositis,[32] or nutritional status prior to transplantation.[33] However, we were able to adjust for other influencing factors, namely, hematological cancer diagnosis,[31] transplant source,[31] and complications.[29,30] Future interventional studies and randomized controlled trials will be necessary to verify the effects of pre-transplant rehabilitation on post-transplant hospital LOS.

In conclusion, pre-transplant rehabilitation for patients with hematologic malignancy scheduled to undergo allo-HSCT may help shorten post-transplant hospital LOS. Consequently, it may be necessary to consider starting rehabilitation before transplantation.

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CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

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