



Original Article

Safety of rehabilitation interventions for patients with hematologic diseases associated with low blood counts—verification focusing on blood cancer

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Abstract. [Purpose] This study aimed to establish unique criteria for hematologic patients with low blood counts in the borderline region of or below the threshold for discontinuing cancer rehabilitation without meeting the criteria for blood transfusion, and to investigate the physical symptoms and activities of daily living. [Participants and Methods] Among the 251 participants, 128 had blood test results below the discontinuation criteria. They were permitted to engage in rehabilitation interventions by a hematologist based on the new criteria. The remaining 123 patients were classified under the discontinuation group. The Barthel Index scores during admission and discharge were compared between the two groups, in terms of chemotherapy, physical symptoms of nausea, petechial hemorrhage, pyrexia, and diarrhea. [Results] There was no significant difference between the two groups in terms of the Barthel Index score during admission or discharge. Pyrexia occurred more frequently in patients managed under the new criteria. [Conclusion] Patients with low blood counts that fall between the criteria for discontinuing rehabilitation and receiving blood transfusions can continue undergoing rehabilitation interventions with the permission of their doctors, provided that measures are taken to manage adverse events. This strategy prevents activities of daily living reduction.

Key words: Hematology, Blood cancer rehabilitation, Criteria for discontinuation criteria

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INTRODUCTION

The blood test-based criteria for discontinuing rehabilitation by cancer patients in Japan are the white blood cell (WBC) count $\leq 3,000/\mu\text{L}$, hemoglobin (Hb) level ≤ 7.5 g/dL, and platelet (Plt) count $\leq 20,000/\mu\text{L}^{1-3}$. The criteria for discontinuing rehabilitation on blood sampling data for cancer diseases overseas are neutrophils $\leq 1,500/\mu\text{L}$, Hb ≤ 7.5 or 8.0 g/dL, and Plt $\leq 20,000/\mu\text{L}^{4-6}$. According to the guidelines for the use of blood products, regarding red blood cell (RBC) transfusions in case of low Hb levels, the recommended Hb level is 6–7 g/dL for anemia associated with hematopoietic failure and 7–8 g/dL for anemia associated with chemotherapy or hematopoietic stem cell transplantation in hematopoietic malignancy. Concerning platelet concentrates (PC) transfusions for low Plt counts, the recommended Plt count is 5,000/ μL for aplastic anemia and myelodysplastic syndrome, and preventive action is recommended in patients with hematopoietic malignancy who are in a stable condition or whose Plt count has not rapidly decreased if it declines to $< 10,000/\mu\text{L}^7$, with blood transfusion not indicated even at levels below the criteria for discontinuing rehabilitation.

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This has led to situations arising in clinical cancer rehabilitation and hematologic disease treatment in which some patients who meet the criteria for discontinuing cancer rehabilitation are nevertheless ineligible for blood transfusions despite having discontinued rehabilitation, and this further diminishes their activities of daily living (ADL).

Regarding rehabilitation interventions in patients with low blood counts, they are recommended for patients undergoing hematopoietic stem cell transplantation from the pretreatment phase to during and after transplantation, to prevent reduced ADL and maintain and improve the quality of life (QOL)¹⁾. In terms of studies of rehabilitation interventions with patients whose Plt count is below the criterion for discontinuation, a study on the safety of exercise interventions for patients with acute leukemia or aggressive lymphoma found that no patient with a Plt count of <10,000/ μ L developed hemorrhage⁸⁾.

The effectiveness of rehabilitation interventions in patients with low blood counts has thus been previously reported, suggesting that it may be possible for such patients to continue rehabilitation interventions even when their blood counts are below the criteria for discontinuation.

This study aimed to establish new criteria for patients with hematologic diseases who meet the existing criteria for discontinuing rehabilitation but are not eligible for blood transfusions to permit them to continue rehabilitation after consultation with a specialist and investigate the effectiveness and safety of rehabilitation interventions conducted under these conditions. Therefore, we investigated the status of rehabilitation interventions, length of hospital stay, physical symptoms, chemotherapy and ADL status.

PARTICIPANTS AND METHODS

We conducted a retrospective study of the electronic medical records of 452 patients who were admitted to the Department of Hematology of Hakodate Municipal Hospital and underwent rehabilitation interventions between April 2017 and March 2019. Patients were excluded if a request for rehabilitation had been submitted but was not implemented, their hospital stay extended across the break between the financial years, they died in the hospital, or their hospital stay exceeded 180 days.

Between April 2017 and March 2018, the criteria for discontinuing rehabilitation comprised the WBC count $\leq 3,000/\mu$ L, Hb level ≤ 7.5 /g/dL, and Plt count $\leq 20,000/\mu$ L, and patients who met these criteria in this period comprised the discontinued group. From April 2018 to March 2019, a framework was established to permit patients with low blood counts, who met the new criteria shown below (Table 1), to continue rehabilitation after their condition had been individually confirmed by a doctor even if their blood counts were in the borderline region below the criteria for discontinuing rehabilitation without

Table 1. Criteria for hematology rehabilitation intervention in our hospital

Criteria for discontinuing hematologic rehabilitation interventions in our hospital	
1.	Platelet count $\leq 10,000/\mu$ L
2.	Hemoglobin level ≤ 6.0 g/dL
3.	Pyrexia $>38^\circ\text{C}$
4.	Patients undergoing bone marrow transplantation
5.	On the day of radiotherapy before bone marrow transplantation
6.	After bone marrow puncture or intrathecal chemotherapy
7.	Hemodynamic instability/poor oxygenation
8.	Severe symptoms of nausea/vomiting or diarrhea
9.	Insufficiently calm or compliant regarding instructions to receive treatment
10.	Uncontrolled pain
11.	Active hemorrhage
If pyrexia is due to pneumonia, respiratory physiotherapy intervention should be considered.	
Criteria for discontinuing hematologic rehabilitation interventions in our hospital if a hematologist is required to decide whether to continue	
1.	Platelet count 10,000–20,000/ μ L
2.	Hemoglobin level 6.0–7.5 g/dL
3.	Platelet count and hemoglobin level are within normal limits but rapidly decreasing
4.	Patients undergoing transplantation pretreatment
5.	Patients present in a clean room following transplantation
6.	Patients undergoing initial chemotherapy for which monitoring is required
7.	Insufficiently calm or compliant with instructions to receive treatment
8.	Uncontrolled pain
9.	Active hemorrhage

meeting the criteria for blood transfusion (Hb levels 6.0–7.5 g/dL and Plt counts 5,000–20,000/ μ L), and these patients were investigated as the new criteria group.

We investigated the age, gender, diagnosis, chemotherapy, length of hospital stay, number of days during which rehabilitation interventions were conducted, and frequency of rehabilitation interventions during admission. The WBC count, Hb level, and Plt count were evaluated using blood test data. ADL were investigated using the Barthel Index (BI) on admission and discharge. Physical symptoms classified as adverse events were handled in accordance with the Common Terminology Criteria for Adverse Events⁹⁾, and the occurrence of pyrexia (>38 °C), petechial hemorrhage, nausea, and diarrhea were investigated.

The BI score on admission and discharge, frequency of rehabilitation interventions, and length of hospital stay were investigated using a t-test. The presence or absence of chemotherapy and the occurrence of physical symptoms of nausea, petechiae, fever, and diarrhea were investigated using a χ^2 test. SPSS for Windows Version 22 (IBM, Tokyo, Japan) was used for statistical analysis, with a $p < 0.05$, regarded as significant.

This study was approved by the Hakodate Municipal Hospital Ethics Committee (approval number: Rapid 2018-73) and the Hirosaki University School of Medicine Graduate School of Health Sciences Ethics Committee (approval number: 2018-044).

RESULTS

Between April 2017 and March 2018, 221 patients received rehabilitation requests. After the exclusion of five patients who did not undergo rehabilitation interventions, one who was still hospitalized at the end of the financial year, 26 who died, and two who were hospitalized for more than 180 days, the remaining 187 patients were included in the study, of whom 123 met the criteria for discontinuing rehabilitation (discontinuation group). The average age of patients in this group was 68.5 years (± 15.0), and they comprised 60 males and 63 females (Table 2).

From April 2018 to March 2019, 231 patients received rehabilitation requests. After the exclusion of seven who did not undergo rehabilitation interventions, five who were still hospitalized at the end of the financial year, 22 who died, and two who were hospitalized for more than 180 days, the remaining 195 patients were included in the study, of whom 128 met the criteria for discontinuing rehabilitation but were permitted to continue by a hematologist (new criteria group). The average age of patients in the new criteria group was 66.8 years (± 16.3), and they comprised 60 males and 68 females.

Malignant lymphoma was the most common diagnosis between April 2017 and March 2018 and April 2018–March 2019 (Table 2).

The number of chemotherapy treatments was 81 in the discontinuation group and 99 in the new criteria group. There was a significant difference in the number of patients who received chemotherapy in the new criteria group (Table 2).

The BI score on discharge was higher in the new criteria group than in the discontinued group, although the differences between their BI scores on admission and discharge were not statistically significant. There was no significant difference in the rate of rehabilitation interventions. The length of hospital stay was significantly shorter in the new criteria group ($p = 0.05$) (Table 3) than in the discontinued group.

There was no significant difference in the occurrence of physical symptoms of nausea, diarrhea, or petechial hemorrhage, with only the incidence of pyrexia being significantly higher in the new criteria group ($p = 0.002$) (Table 3) than in the discontinued group. There were no adverse events, such as falls or fractures due to rehabilitation interventions in either group.

DISCUSSION

A comparison between the discontinued and new criteria groups showed that the length of hospital stay was significantly shorter in the latter group than in the former. This result is thought to reflect the fact that these patients continued rehabilitation interventions despite meeting the criteria for discontinuation. The BI score on discharge was also higher in the new criteria group than in the discontinued group, although this difference was not statistically significant, suggesting that rehabilitation may have helped prevent a reduction in ADL. These findings suggest that if patients who meet the criteria for discontinuing rehabilitation interventions continue rehabilitation with their doctor's permission, this may improve their care QOL, prevent a reduction in ADL, and maintain or improve motor functions, enabling them to spend a reduced amount of time in the hospital.

Since patients with hematologic diseases exhibit low blood counts during treatment and their level of physical activity diminishes, it is recommended that they undergo exercise therapy interventions to prevent a reduction in ADL¹⁾. The Japanese Clinical Practice Guidelines for Cancer Rehabilitation recommend exercise rehabilitation interventions for post-chemotherapy patients¹⁰⁾, and aerobic exercise and muscle training are recommended as effective exercise therapy for patients who undergo transplantation^{10–12)}. A systematic review by Bergental et al. found that there had been no reported increase in adverse events as a result of exercise therapy for patients with hematopoietic stem cell transplantation, and although hemorrhage, pyrexia, pneumonia, deep venous thrombosis, infection, and other adverse events did occur in patients with hematopoietic malignancies during aerobic exercise, there was no statistically significant difference¹³⁾. The American College of Sports Medicine reported that exercise therapy interventions for patients with lymphoma had no effect on the

Table 2. Patient demographics

	Discontinued group (n=123)	New Criteria group (n=128)
Demographics		
Age (years)	68.5 (± 15.0)	66.8 (± 16.3)
Gender (male/female)	60/63	60/68
Height (cm)	158.7 (± 10.7)	158.5 (± 10.5)
Body weight (kg)	54.0 (± 12.3)	55.4 (± 11.8)
Diagnosis		
Malignant lymphoma	50	40
Multiple myeloma	16	19
Myelodysplastic syndrome	23	16
Acute lymphoblastic leukemia	16	21
Acute myeloid leukemia	6	14
Others	12	18
Chemotherapy	81	99*

Average (standard deviation).

*p<0.05.

Table 3. Clinical characteristics and physical symptom

	Discontinued group (n=123)	New criteria group (n=128)
Clinical characteristics		
Barthel Index score on admission	68.9 (± 33.2)	73.8 (± 28.6)
Barthel Index score on discharge	79.4 (± 30.8)	84.4 (± 26.6)
Length of hospital stay (days)	43.3 (± 34.4)	35.4 (± 25.2)*
Rehabilitation intervention rate (%)	58.0 (± 0.2)	61.1 (± 0.2)
Physical symptom		
Nausea	36	39
Petechial hemorrhage	33	23
Pyrexia	90	114*
Diarrhea	54	50

Average (standard deviation).

*p<0.05.

treatment completion rate, and there were no safety issues with exercise therapy during or after transplantation, and they improved the muscle strength and QOL¹⁴).

In the investigation of physical symptoms, only fever was observed in the new standard group, and a significant difference was observed. This may be due to the significant difference in the comparison of chemotherapy treatment. Since patients who meet the criteria for discontinuing rehabilitation have low blood counts resulting from treatments, such as chemotherapy and bone marrow transplantation, the concomitant presence or appearance of some degree of physical symptoms is to be expected, and pyrexia and other side effects of treatment may have contributed to this result. It is vital to understand and monitor individual changes over time during exercise interventions in patients with low blood counts, including disease characteristics, nature of the treatment, and disease duration. Measures must be taken to manage adverse events; thus, understanding their general condition daily and checking their physical assessments are both important so that, if pyrexia occurs, it can be treated.

In a previous study on the criteria for discontinuing rehabilitation when blood counts were low, Miyamura et al.¹⁵) investigated decisions made on physiotherapy for patients receiving allogeneic hematopoietic stem cell transplantation, and found that different institutions used different threshold values for pyrexia and cytopenia when deciding whether to conduct physiotherapy, reporting that the actual practice was to change the status of intervention based on the patient's individual condition rather than using specific criteria.

Uniformly discontinuing rehabilitation interventions for patients with low blood counts solely based on the criteria of their blood test results may reduce their ADL and give rise to secondary complications; therefore, it is important to investigate continued rehabilitation interventions in clinical practice.

One of the blood test-based criteria for discontinuing cancer rehabilitation is a WBC count of $\leq 3,000/\mu\text{L}$, although cases

of rehabilitation intervention for patients with hematopoietic stem cell transplantation whose WBC count is low from pre-treatment to engraftment have been reported. Moreover, this may help prevent a reduction in ADL as well as maintain and improve the QOL^{10–12, 16, 17}). Therefore, whether to continue rehabilitation interventions for patients with a low WBC count is under consideration.

For Hb levels, the criterion for discontinuing rehabilitation is 7.5 g/dL. According to the Japanese Ministry of Health, Labour and Welfare's guidelines for the use of blood products, the recommended Hb level as the trigger for RBC transfusion is 6–7 g/dL for anemia associated with hematopoietic failure and 7–8 g/dL for anemia associated with chemotherapy or hematopoietic stem cell transplantation for hematopoietic malignancy⁷), indicating that some patients who meet the criteria for discontinuing rehabilitation are not eligible for RBC transfusion. Similarly, the Plt count, which is the criterion for discontinuing rehabilitation, is $\leq 20,000/\mu\text{L}$ ^{1–3}), and the Japanese Ministry of Health, Labour and Welfare's guidelines for the use of PC transfusions recommend that the indication for transplantation be set at a Plt count of 5,000/ μL for aplastic anemia and myelodysplastic syndrome and 10,000/ μL for hematopoietic malignancy.⁷) Similar to those for Hb levels, the Plt count criteria for transfusions are also set so that some patients who meet the criteria for discontinuing rehabilitation are ineligible for blood transfusions without receiving rehabilitation interventions.

Challenges in the care of patients with low Plt counts include occurrence of hemorrhagic events due to hemorrhagic tendencies, such as cerebral and visceral hemorrhage, and caution during rehabilitation interventions is therefore required. Among studies on hemorrhagic tendencies in hematologic diseases, one randomized controlled trial of the PC transfusion trigger level found that even reducing this from 20,000/ μL to 10,000/ μL did not decrease the incidence of hemorrhage^{18, 19}). Oka et al.²⁰) reported that in remission induction therapy for acute leukemia, reducing the PC transfusion trigger level from 20,000/ μL to 10,000/ μL decreased the use of PC transfusions without increasing the risk of hemorrhage. Further, they stratified patients undergoing hematopoietic stem cell transplantation into low-, moderate-, or high-risk patients in terms of PC-transfusion-related risk factors and administering prophylactic or therapeutic PC transfusions in accordance with the risk-enabled transfusions²¹). In a narrative review, Morishita et al. suggested that patients with a Plt count of 10,000–20,000/ μL should undergo exercise therapy comprising non-resistance exercises in the seated or standing postures, protective stretching exercises, and walking²²).

Concerning exercise-induced hemorrhagic events, one study on the safety of exercise interventions in patients undergoing intensive chemotherapy for acute leukemia or aggressive lymphoma reported that no patient with a Plt count $< 10,000/\mu\text{L}$ had developed hemorrhage⁸).

Based on the above, the literature includes studies on the indications of blood transfusions in patients with low Hb levels or Plt counts. In addition, reports of hemorrhagic tendencies, trigger values of 7 g/dL for RBC transfusion, and 10,000/ μL for PC transfusion have been suggested as indicators in patients with hematologic disease. However, the use of these as guideline values indicates that some patients whose values are below the criteria for discontinuing rehabilitation but above the blood transfusion trigger levels do not receive blood transfusions, and further investigations of rehabilitation interventions for patients below the current criteria for discontinuation and studies of patients with different diseases are required.

The limitations of this study are that it does not consider disease characteristics and does not examine the effects of the type of chemotherapy. Even based on these facts, it is possible that the length of hospital stay can be shortened by grasping the daily general condition, confirming the physical assessment, and considering continuous rehabilitation intervention without uniformly stopping the rehabilitation intervention based on blood sampling data. I think it was meaningful to show it.

Conflict of interest

There are no conflicts of interest to disclose.

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