

Original Article

Rehabilitation intervention safety in patients with malignant lymphoma with low blood cell counts

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Abstract. [Purpose] We established criteria for patients with malignant lymphoma with low blood counts, who did not meet the criteria to discontinue rehabilitation or the blood transfusion criteria even though they were borderline for discontinuing rehabilitation. We investigated physical symptoms, activities of daily living, and adverse events in patients who were permitted to undergo rehabilitation intervention using the new criteria. [Participants and Methods] Forty-two patients met the criteria to discontinue rehabilitation based on blood data, and the new-criteria group included 153 patients who received permission for rehabilitation from a hematologist despite not meeting the criteria to discontinue rehabilitation. The survey items were Barthel index at the time of admission and discharge and the length of hospital stay. A two-group comparison was performed, and the occurrence of adverse events associated with exercise intervention were investigated. [Results] The length of hospital stay was shortened in the new-criteria group, and the rehabilitation intervention rate improved. [Conclusion] For patients with malignant lymphoma with low blood cell counts, continuing rehabilitation intervention with physician permission may prevent a decline in activities of daily living as well as maintain and improve motor function.

Key words: Malignant lymphoma, Rehabilitation, Discontinuation criteria

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INTRODUCTION

In the clinical setting of rehabilitation for hematologic diseases such as malignant lymphoma, even though blood collection data such as hemoglobin (Hb) levels are below the criteria for discontinuing rehabilitation, exercise therapy is discontinued without any indication for blood transfusion. We experience more than a few cases in which ADL declines.

Therefore, we focused on hematological medical cases such as malignant lymphoma, myelodysplastic syndrome, and multiple myeloma with low blood cell levels. We examined a group of cases that fell below the rehabilitation discontinuation criteria, and we established our own criteria for cases that fell below the rehabilitation discontinuation criteria and did not meet the transfusion criteria but were in the “boundary region” quite close to the transfusion cutoff values. We investigated physical symptoms and ADL in a group of patients who were allowed to undergo rehabilitation intervention. Compared to the rehabilitation discontinuation group, the new criteria group reported a shorter hospitalization period, no decline in ADL function, and no adverse events associated with exercise intervention¹⁾.

However, when all hematologic diseases are grouped together as described above, the characteristics of physical symptoms and the appearance of adverse events differ for each disease, as does the severity of the disease, so therapeutic intervention approaches differ. is expected. In other words, there was an issue of continuing research for each disease.

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Therefore, this time, we will report the results of a survey targeting malignant lymphoma²⁾, for which the number of new cases is increasing year by year in Japan.

The purpose of the current study was to establish new criteria for permitting continuation of rehabilitation after consultation with a specialist in patients who met the criteria for discontinuing rehabilitation but were between the criteria and were not eligible for blood transfusion. We examined the usefulness and safety of rehabilitation intervention when implemented, considering the status of rehabilitation intervention, length of hospital stay, physical symptoms, ADL status, and adverse events.

PARTICIPANTS AND METHODS

A total of 240 patients admitted to the Hematology Department of Hakodate Municipal Hospital, Japan, from April 2017 to March 2021 who were diagnosed with malignant lymphoma and underwent rehabilitation intervention, were included in the study. These patients were retrospectively reviewed using their electronic medical records. Exclusion criteria for participants were as follows: rehabilitation request but no intervention, continuous hospitalization for more than one year, death during hospitalization, or hospitalization period of 180 days or longer. The group of patients that met the criteria for stopping rehabilitation intervention [white blood cell (WBC) 3,000 / μ L, Hb 7.5g/dL, and platelets (Plt) 20,000 / μ L] between April 2017 and March 2018 to was defined as the rehabilitation discontinuation group. A new system was adopted between April 2018 and March 2021 to permit rehabilitation under the new criteria (Tables 1 and 2). Specifically, we defined the new-criteria group as the group of patients that fell below the rehabilitation discontinuation criteria and also did not meet the transfusion criteria but were within a boundary range (Hb: 6.0–7.5 g/dL, Plt: 5,000–20,000 / μ L); while in this state, they received permission to continue rehabilitation intervention after individual consultation with a physician to confirm their status.

To prevent infection when the white blood cell level was low, the range of activities when the neutrophil level was 500 / μ L or less was limited to the patient's own room, and when the prednisone dose was 30 mg/day or more, the range of activities was limited to the ward.

Exercise intervention was performed on the basis of 20 minutes or more a day, 5 days a week. As for the type of exercise,

Table 1. Criteria for hematology rehabilitation intervention in our hospital

| Criteria for discontinuing hematologic rehabilitation interventions in our hospital |
|---|
| 1. Platelet count $\leq 10,000/\mu\text{L}$ |
| 2. Hemoglobin level ≤ 6.0 g/dL |
| 3. Pyrexia $\geq 38^\circ\text{C}^\#$ |
| 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.

Table 2. Criteria for hematology rehabilitation intervention in our hospital

| 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/ μL |
| 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 |
| 10. Petechial hemorrhage or other signs suggestive of hemorrhagic tendency |

the physiotherapist in charge selected endurance exercise and muscle strengthening exercise based on blood sampling results and physical symptoms. For endurance exercises, they performed bicycle ergometer and walking, and for muscle exercises, they performed bodyweight squats, calf raises, and manual resistance exercises.

The survey items included: age, gender, length of hospitalization, number of days from the start of rehabilitation intervention to the date of discharge, and frequency of rehabilitation intervention. WBC, Hb, and Plt values were investigated in blood collection data. For ADL, we surveyed BI at admission and discharge. Physical symptoms were investigated according to the CTCAE criteria³⁾, and the presence or absence of vomiting, pyrexia (>38°C), petechiae, and diarrhea was recorded. We also investigated the occurrence of adverse events associated with exercise intervention in the new-criteria group.

In the analysis of each survey item, the Shapiro–Wilk test was used to confirm the normality of the data. Since no normality was observed, the Mann–Whitney U test was performed on admission and discharge BI, frequency of rehabilitation interventions, and length of stay. A χ^2 test was performed for the presence or absence of physical symptoms such as nausea, fever, petechiae, and diarrhea. Statistical processing was performed using SPSS for Windows Ver24 (manufactured by IBM, Tokyo, Japan) with a significance level of 5% or less. This study was conducted with the approval of the Hakodate Municipal Hospital Ethics Committee (approval number: Jin 2018-73) and the approval of the Hirosaki University Graduate School of Health Sciences Ethics Committee (approval number: 2018-044).

RESULTS

Between April 2017 and March 2018, 54 cases were requested for rehabilitation. Exclusions were: no intervention (5), deaths (4), and hospitalizations >180 days (2). Ultimately, 43 cases met the criteria for discontinuing rehabilitation. The median age of the non-rehabilitation group was 75 [63–83.25] years, with 21 males and 22 females (Table 3).

A total of 186 cases were requested for rehabilitation between April 2018 and March 2021. A total of 153 patients were included (six patients who did not receive rehabilitation intervention and 27 who died were excluded). All patients were below the criteria for discontinuing rehabilitation, and permission for rehabilitation intervention was required from the hematology physician. The median age of the new criteria group was 72 [62–78] years, with 75 males and 78 females.

The BI values at admission and at discharge in the new-criteria group were higher than those in the discontinued group, but there was no statistically significant difference in the comparison of BI values at admission and discharge. The length of hospital stay in the new-criteria group was shortened from 28.5 days to 24 days, compared to the rehabilitation discontinuation group ($p=0.027$). Regarding the rehabilitation intervention rate, the new-criteria group improved from 62% to 63% compared to the rehabilitation discontinuation group ($p=0.047$) (Table 3). As for the incidence of physical symptoms, Pyrexia and diarrhea were observed. More than two-thirds of the patients in both groups had pyrexia symptoms, and half of them had diarrhea. Nausea was observed in about 30% of both groups. A survey of physical symptoms showed no significant differences in nausea, pyrexia, petechiae, and diarrhea (Table 3). There were no adverse events such as falls and fractures due to exercise therapy intervention in the new criteria cases. There were no adverse events associated with exercise intervention in both groups.

Table 3. Patient demographics

| | Discontinued group (n=43) | New criteria group (n=153) |
|--------------------------------------|---------------------------|----------------------------|
| Demographics | | |
| Age (years) | 75 [63–83.25] | 72 [62–78] |
| Gender (male/female) | 21/22 | 75/78 |
| Clinical characteristics | | |
| Barthel Index score on admission | 80 [18.75–90] | 85 [35–95] |
| Barthel Index score on discharge | 85 [63.75–100] | 90 [50–100] |
| Length of hospital stay (days) | 28.5 [21–41.25] | 24* [15.5–34.50] |
| Rehabilitation intervention rate (%) | 62 [46–70] | 63* [55–70] |
| Chemotherapy | 23 | 95 |
| Physical symptom | | |
| Nausea | 12 | 46 |
| Petechial hemorrhage | 7 | 22 |
| Pyrexia | 34 | 103 |
| Diarrhea | 19 | 83 |

Median (Interquartile Range).

* $p<0.05$.

DISCUSSION

The survey results for malignant lymphoma did not differ significantly from the results for blood diseases as a whole shown in previous studies, and there were few specific aspects or characteristics regarding physical symptoms and adverse events. It was suggested that the hospitalization period could be shortened.

In this study, we set new criteria for rehabilitation interventions for patients with low blood cell counts. The reference values for WBC, Hb, and Plt for rehabilitation intervention were set with reference to the following literature.

In a report on physiotherapy intervention criteria for low blood cell levels in Japan, Miyamura et al.⁴⁾ investigated whether to implement physical therapy for patients with allogeneic hematopoietic cell transplants. They reported that when the hemoglobin value ranged from 6.0–8.0 g/dL, the amount of exercise was reduced and rehabilitation interventions, which differed among facilities, were performed after blood transfusion. Similarly, for platelet levels from 10,000–30,000 / μ L, each institution responded differently, such as performing aerobic exercise or performing rehabilitation intervention after blood transfusion.

A report on rehabilitation intervention with a WBC value below the standard value for discontinuation of rehabilitation found that by responding to side effects and changes in the general condition associated with treatment, improvement in physical function and alleviation of symptoms such as cancer-related malaise were observed^{5–7)}. In addition, in rehabilitation for hematopoietic stem cell transplant patients, there is a report of rehabilitation intervention when the WBC level is low during the period from pretreatment to engraftment, and efforts are being made to prevent decline in ADL ability and to maintain and improve QOL^{6–10)}.

On the other hand, there are no reports on rehabilitation intervention for patients whose Hb level is below the criteria for discontinuing rehabilitation. However, according to the Japanese Ministry of Health, Labor and Welfare guidelines for the use of blood products, RBC (Red Blood Cells) transfusion trigger value is 6 to 7 g/dL for anemia associated with hematopoietic insufficiency, and Hb value is 6 to 7 g/dL for hematopoietic tumors and chemotherapy and hematopoietic stem cell transplantation treatment. Hb value 7–8 g/dL is recommended for anemia caused by such factors as¹¹⁾, and there are cases in which RBC transfusion is not indicated even if the criteria for stopping rehabilitation are not met. The American Association of Blood Banks (AABB) transfusion guidelines recommend an Hb level of 7.0 g/dL as the trigger value for RBC transfusion in hemodynamically stable adult patients. For thrombocytopenia, detailed transfusion criteria have not been presented¹²⁾.

The criteria for discontinuing rehabilitation of Plt values are Plt 20,000/ μ L^{13–15)}. According to the guidelines for use of blood products mentioned above, Plt values are 5,000/ μ L in aplastic anemia and myelodysplastic syndrome, and hematopoietic tumors recommended 10,000/ μ L for transfusion¹¹⁾. As described above, there are cases in which blood transfusion is not indicated and rehabilitation intervention is not performed when the Plt value is below the criteria for cessation of rehabilitation.

Problems in treatment when Plt is low include bleeding events such as cerebral hemorrhage and organ hemorrhage due to susceptibility to bleeding, and caution is required in rehabilitation intervention. The AABB Platelet Concentrate (PC) transfusion criteria recommend a Plt value of 10,000/ μ L to prevent bleeding complications during myelosuppression¹⁶⁾. A randomized controlled trial (RCT) of PC transfusion trigger levels reported that there was no difference in the frequency of bleeding when the level was lowered from 20,000/ μ L to 10,000/ μ L^{17, 18)}. A study of transfusion trigger levels and number of transfusions in the American Society of Clinical Oncology (ASCO) compared trigger levels for prophylactic PC transfusions in patients with hematological malignancies of 20,000/ μ L and 10,000/ μ L, with They reported that the number of blood transfusions decreased without increasing the risk of bleeding even at 10,000/ μ L¹⁹⁾. In Japan, Oka et al.²⁰⁾ reported that in the induction therapy of acute leukemia, even if the trigger level of PC transfusion is set from 20,000/ μ L to 10,000/ μ L, the risk of bleeding does not increase and PC transfusion can be reduced.

Hematopoietic stem cell transplantation cases are stratified into low, moderate, and high-risk patients according to factors related to PC transfusion, and it is reported that appropriate blood transfusion is possible by performing preventive and therapeutic PC transfusion according to risk is doing²¹⁾. A study on the safety of exercise intervention in patients with acute leukemia or advanced lymphoma reported that none of the patients with a Plt value of less than 10,000/ μ L experienced bleeding⁵⁾.

It was speculated that this point would be the reason for the new rehabilitation intervention criteria for low blood cell counts.

A significant difference was observed in the length of hospital stay and rate of intervention in rehabilitation between the rehabilitation discontinuation group and the new-criteria group. This result is considered to be due to the improvement of the rehabilitation intervention rate and the shortening of the hospitalization period as an effect of continuing rehabilitation intervention for cases below the threshold for stopping rehabilitation. Pyrexia and diarrhea are the most frequent occurrences of physical symptoms, which should be taken into consideration when considering continuous rehabilitation intervention.

There was no statistically significant difference in comparing discharge BI. However, the discharge BI value was higher in the new criteria group than in the rehabilitation discontinuation group. This is thought to be due to the prevention of decline in ADL and the maintenance of motor function without motor function deterioration by performing rehabilitation intervention for patients with low blood cell counts.

Based on these results, continuing rehabilitation intervention for malignant lymphoma cases below the threshold for stopping rehabilitation with doctor's permission will lead to an improvement in quality of life during recuperation, prevention of decline in ADL, and maintenance and improvement of motor function. Furthermore, it may have contributed to an improvement in rehabilitation intervention rate and a reduction in hospital stay.

With regard to rehabilitation interventions for hematology cases, exercise therapy interventions are recommended for the purpose of preventing decline in ADL because hematological tumors exhibit low blood cell counts and reduced physical activity during the course of treatment¹³⁾. Cancer rehabilitation clinical practice guidelines recommend exercise therapy intervention for patients after chemotherapy treatment²²⁾. Aerobic exercise and strength training are recommended for transplant patients^{9, 10, 22)}.

In cases where hematopoietic function has declined and blood counts are unlikely to recover and the blood count is below the standard value for rehabilitation, rehabilitation intervention will not be implemented unless blood transfusion therapy is implemented. For this reason, uniformly discontinuing rehabilitation intervention based only on the blood sampling data may decrease ADL and cause secondary complications. Therefore, it is clinically important to consider continuous rehabilitation interventions. In the current survey of physical symptoms, there was no significant difference between the rehabilitation discontinuation group and the new-criteria group, and no adverse events were associated with exercise intervention in the new-criteria group. Continuous rehabilitation intervention can therefore be considered by setting intervention criteria for cases below the rehabilitation discontinuation criteria.

Kasahara et al.²³⁾ reported that there were no adverse events due to physical therapy intervention in a survey on exercise intervention for malignant lymphoma cases with cytopenia.

To consider continued exercise intervention in the setting of low blood cell counts, we should understand and confirm changes over time for each case, including physical symptoms and information such as disease characteristics, treatment details, and disease duration. Physical symptoms such as nausea, pyrexia, and diarrhea, are common, especially in rehabilitation for hematology cases where bone marrow transplantation, radiotherapy, and chemotherapy are performed. In addition, it is necessary to consider the risk of bleeding events due to thrombocytopenia and infection prevention with leukopenia. Therefore, daily confirmation of blood sampling results and physical symptoms is essential, and it is necessary to select exercise items according to each patient's condition.

Problems in medical treatment when Plt is low include bleeding events such as cerebral hemorrhage and organ hemorrhage due to hemorrhage susceptibility, and caution is required in rehabilitation intervention. A review by Morishita et al.²⁴⁾ suggested exercise therapy for patients with platelets of 10,000–20,000/ μ L, including exercise without resistance in sitting or standing positions, gentle stretching exercises, and walking.

As described above, there are reports on exercise intervention when Hb and Plt are low^{4, 17, 23–25)}. Continuing rehabilitation intervention for patients with hematologic diseases presenting with low blood cell levels may be considered possible by checking the blood collection data and adjusting the type of exercise and exercise load.

In a previous study¹⁾ and in this study, we examined continuous rehabilitation intervention after consultation with a hematologist. As a result, the patient's motor function was maintained without any adverse events associated with exercise intervention, suggesting the possibility of continuous rehabilitation intervention for hematology patients with low blood cell counts. Limitations of this study include the fact that this study did not limit the type of exercise and exercise load, and that it was a single-center study. In the future, it is necessary to consider exercise therapy that can be safely carried out, such as selection of exercise items according to low blood cell levels and physical symptoms, setting of exercise load, and joint research with other institutions.

Conflict of interest

There are no conflicts of interest to disclose in this study.

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