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Research Article

Second Allogeneic Stem Cell Transplantation in Acute Leukemia with Post-Transplantation Relapse

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Abstract

Aim: It is known that the prognosis of acute leukemia patients who relapse after the first allogeneic stem cell transplantation (ASCT) is dismal. Our goal was to assess the value of a second allogeneic stem cell transplant in acute leukemia patients who experienced post-transplant recurrence.

Material and Methods: We retrospectively reviewed data from 29 patients with relapsing acute leukemia who underwent a second ASCT. Nineteen patients with acute myeloid leukemia and ten patients with acute lymphoblastic leukemia were included in the study.

Results: Ten AML patients and 10 ALL patients were included in the study. Most patients (62%) were in remission before the second transplantation. The median time between the first and second ASCT was 11.9 months (3.1-42 months). Complete remission (CR) was achieved after the second ASCT in 21 (72%) patients, and 11 (52%) patients relapsed after the second ASCT. During this analysis, six patients (21%) were alive and in remission. Relapse of the disease was the leading cause of mortality. After the second ASCT, overall survival (OS) was 6.34 months, and leukemia-free survival (LFS) was 13.8 months.

Conclusion: For patients with acute leukemia who relapsed after the first ASCT, a second ASCT is a good option and can keep patients alive.

Keywords: Post transplantation relapse, second transplantation, acute leukemia

INTRODUCTION

In order to effectively treat acute leukemias, allogeneic stem cell transplantation (ASCT) is an indispensable step. Unfortunately, the results are poor, and clinicians may occasionally encounter post-transplant relapse and graft failure (1-3). Leukemia patients who develop relapse after ASCT have a brief life span (4). There is no standardized method in their management. One of the treatment approaches is second allogeneic stem cell transplantation (5). But the second ASCT may be more complex than the first due to increased drug side effects and comorbidities (6). Nevertheless, studies have shown that second allogeneic stem cell transplantation is more beneficial than post-relapse chemotherapy (7).

We want to share our single-center experience with acute leukemia patients who underwent a second ASCT following a first allogeneic stem cell transplant due to relapse in this study.

MATERIAL AND METHOD

In this article, we discuss our single-center experience with second ASCT to treat patients with acute leukemia relapse after a first ASCT. Written and signed consents were obtained from the patients included in the study,

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which was approved by the Ethics Committee of Erciyes University (2020/148-26.02.2020).

Patients

The data of patients with acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL) who underwent second allogeneic transplantation due to relapse after the first allogeneic transplantation at Erciyes University Bone Marrow Transplantation and Stem Cell Center were retrospectively analyzed. Patients who had a second transplantation due to engraftment failure after the first transplantation were excluded from this study. The study involved 29 patients who were followed between 2010 and 2019. The patients' performance status before the second transplantation was determined according to the Eastern Cooperative Oncology Group (ECOG) performance score (8). Patients were classified according to the HCT-comorbidity index (HCT-CI) in terms of comorbidities before the second transplantation (9). Before starting the second transplant's conditioning regimen, the patients' serum ferritin, albumin, and total blood count values were recorded.

HLA-Typing and Donors

Granulocyte-colony stimulating factor (G-CSF) was applied for graft mobilization in both transplantations, and peripheral stem cells were used as the graft source. The high-resolution molecular typing method was used in HLA typing (HLA-A, HLA-B, HLA-C, HLA-DRB1, and HLA-DQB1) of both patients and donors. As donors, 10/10 HLA matched relative, 9/10 HLA matched relative, full match unrelated, and haploidentical relative donors were used.

Definitions

After HSCT, a blast count >5% in bone marrow was determined as a relapse. In evaluating remission status before transplantation, complete remission (CR) was described as <5% blast in bone marrow, absence of blast in peripheral blood, absence of extramedullary disease, and absolute neutrophil count ≥1.0 × 109 / L, platelet count 100×109/L. Active disease was defined as 5% blasts in the bone marrow, the presence of blasts in peripheral blood, or the development of extramedullary disease. (10) Peripheral complete blood count was used to evaluate engraftment. Neutrophil engraftment was defined as the first day when the absolute neutrophil count (ANC) was ≥ 0.5×109/L. Platelet engraftment was defined as the first day of more than 20 × 109/L for two consecutive days without platelet transfusion. Overall survival (OS) was calculated from the second ASCT to death or last follow-up. The leukemia-free survival (LFS) time was calculated from the second ASCT to the disease relapse date.

Conditioning Regimens and GVHD Prophylaxis

The classification defined by Bacigalupo et al. served for assessing the intensity of the conditioning regimens (11). In all patients, cyclosporine was preferred for graft-versus-host disease (GVHD) prophylaxis. Patients were evaluated and graded for acute and chronic GVHD (12,13).

Statistic

Continuous data matching normal distribution were expressed as mean ± standard deviation, continuous data not matching normal distribution as median and min-max, and categorical data as percentages (%). Categorical data were compared using the Chi-square test. The end points of our study were OS and LFS after the second ASCT. Survival curves were created by the Kaplan-Meier method. The data were analyzed with the SPSS for Windows package software program (v. 22.0, SPSS Inc., Chicago, IL, USA). A p-value < 0.05 was considered significant.

RESULTS

Table 1 provides an overview of the characteristics of 29 patients.

Table 1. Clinical characteristics of patients

Characteristics	Total n=29 n (%)
Age, year, median (range)	37 (17-67)
Sex	
Male	18 (62)
Female	11 (38)
Disease	
AML	19 (66)
ALL	10 (34)
Disease status at second HSCT	
Remission	18 (62)
Active	11(38)
HCT comorbidity index	
0-1	18 (62)
>2	11 (38)
Donor type	
Same	14
Different	15
Remission duration of first HSCT, months, median (range)	8.2 (1-24.6)
Median time from first to second HSCT, months (range)	11.9 (3.-42)
HLA Type	
Full matched	18 (62)
Haploidentical	11 (38)
Conditioning intensity	
MAC	17 (59)
RIC	12 (41)
Acute GVHD (grade 2-4)	
Yes	7 (24)
No	22 (76)
Chronic GVHD	
Yes	2 (7)
No	27 (93)

AML: Acute myeloid leukemia, ALL:Acute lymphoblastic leukemia, HSCT: Hematopoietic stem cell transplantation, GVHD:Graft versus host disease, MAC: myeloablative regimen
RIC: reduced intensity regimen

Flow diagram of 29 patients who underwent second ASCT is shown in Figure 1. The median age at the second transplantation was 37 (17-67). Eighteen (62%) patients were male, and eleven (38%) were female. Nineteen (66%) and ten (34%) of the study patient population were AML and ALL, respectively. Most patients (62%) were in remission before the second transplantation. The median time between the first and second ASCT was 11.9 months (3.1-42 months). Fifteen patients underwent the second ASCT with a different donor. As conditioning regimens, myeloablative conditioning (MAC) regimens were preferred in 17 (59%) patients, and reduced intensity conditioning (RIC) regimens were preferred in 12 (41%) patients. Engraftment was performed in 22 (76%) patients. In these patients, median neutrophil engraftment occurred in 18th days and platelet engraftment in 17th days. Seven patients died before engraftment. One patient engrafted with active disease.

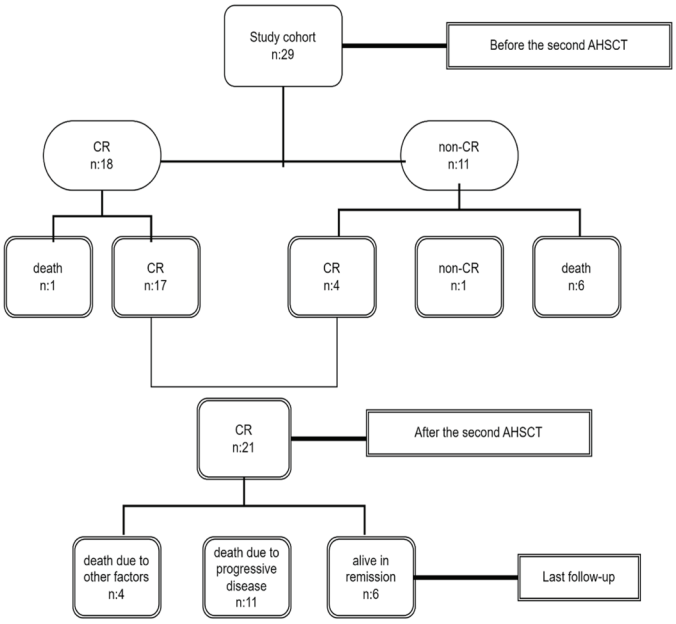

Figure 1. Flow diagram of 29 patients who underwent a second AHSCT

Engraftment did not occur in 6 of 11 patients with the active disease before the second ASCT. Control bone marrow evaluation of 4 out of 5 patients with engraftment resulted in remission. Considering all patients, complete remission (CR) was achieved after the second ASCT in 21 (72%) patients. Eleven (52%) patients relapsed after the second ASCT. The median time from the second ASCT to relapse was 7.5 months (1.4-16.2 months).

A total of six patients (21%) were alive and in remission at the time of this analysis. The median overall survival was 6.34 months (0.2-99.9 months). Overall survival was calculated as 62%, 41%, and 22% at day 100, month 12, and month 18 by the Kaplan-Meier survival analysis, respectively (Figure-3). Median leukemia-free survival was 13.8 months (range, 0-99.9 months). The probabilities of LFS at 100 days, 12 months, and 18 months were 80.7%, 55.2%, and 27.6%, respectively (Figure-2). Of the 29 patients included in the study, 23 died. Considering the causes of death, the most common reason was disease relapse. The median follow-up duration was 29 months (8-100.5 months).

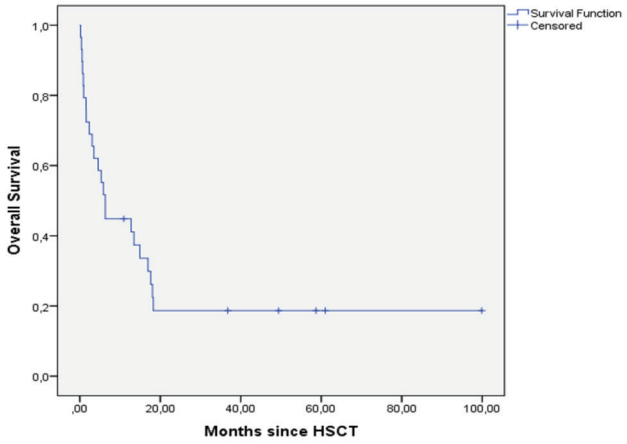

Figure 2. Overall survival of study cohort

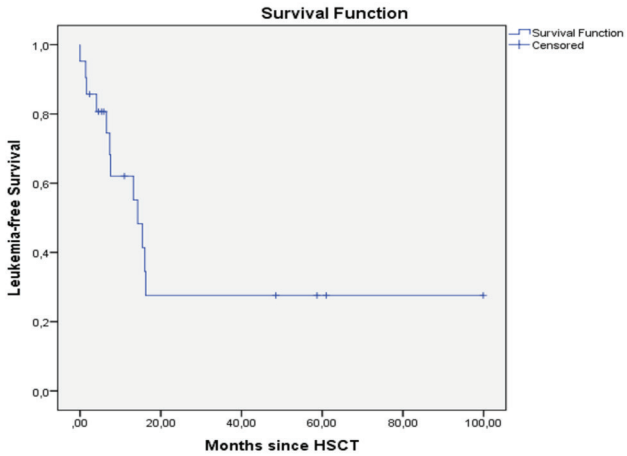

Figure 3. Leukemia-free survival of study cohort

DISCUSSION

The primary cause of treatment failure following allogeneic transplantation is acute leukemia relapse, a considerable problem. Patients with high-risk diseases have several critical treatment options, including second allogeneic transplantation. It is known that active disease during transplantation negatively affects the results of transplantation (14,15). Eleven patients with active disease were transplanted in our study, and four of these patients achieved complete remission. Engraftment did not occur in six patients. On the other hand, 17 of 18 patients with disease in remission were engrafted and followed up with complete remission. Therefore, the pre-transplant disease burden seems to be an essential factor affecting the success of the transplant. However, we think there is a great chance to achieve complete remission after transplantation in patients with active disease.

The same or different donor can be used in the second transplantation. No survival benefit from using a new

donor has been demonstrated in the literature (16-18). In our study, a different donor was used in half of the patients. The results were similar in terms of overall survival and leukemia-free survival. To benefit from the graft versus leukemia effect, switching to a haploidentical donor may improve the success of the transplantation (19, 20). However, the small number of patients in our study made it impossible to evaluate this.

There are conflicting results in studies showing the effects of GVHD in preventing relapse (21,22). Acute GVHD, LFS, and OS had no statistically significant correlation in our study. Likewise, there was no statistically significant correlation between chronic GVHD and LFS or OS.

In some studies, a longer time interval between the first ASCT and the second ASCT has been shown to affect survival positively. In our study, 15 and 14 patients relapsed before and after one year (15,16,23). Leukemia-free survival and OS were similar in both groups.

In a study conducted by Hazar et al. in a pediatric group of 51 patients, the complete response rate was 80.4% (24). In our study, the CR was found to be 72%. In the same study, 1-year OS was calculated as 42% and 1-year LFS as 36.9% (24). The results were similar to our research. In another study, OS was 35%, and 2-year LFS and OS were 32%, with a mean follow-up of 64 months (3).

Our study has limitations, such as the small patient group and retrospective nature.

CONCLUSION

As a result, a second transplantation still holds its place to achieve remission in these patients, whose treatment options are minimal. Even if the survival rate is not high, it is promising that six of our patients lived longer than two years after transplantation and remained in remission. Patients who were in remission before the second transplantation had a better prognosis than those who were not in remission. Among leukemia-free survivors after the second transplantation, disease relapse was the most common cause of treatment failure. Furthermore, after the second ASCT, the patients suffered from severe toxicities. We think relapse prevention methods are needed first to improve the outcomes of patients who relapse after transplantation.

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