



Original Research

Second allogeneic stem cell transplantation in acute leukemia patients: single-centre experience

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HIGHLIGHTS

- Relapsed acute leukaemia after the first allogeneic stem cell transplantation has a poor prognosis.
- Second allogeneic transplantation may offer survival advantage for relapsed leukaemias.

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ABSTRACT

Acute leukaemia patients who relapse after the first allogeneic stem cell transplantation (Allo-SCT) have a poor prognosis. Participating in clinical trials is the best option for these patients. If patients cannot participate in clinical trials, as the treatment options are limited, the second allo-SCT constitutes the potential curative treatment option. The data of acute leukaemia patients who underwent second allo-SCT because of relapsed/refractory disease after the first allo-SCT at our centre between December 2009 and February 2019 were analyzed retrospectively. Three hundred nineteen acute leukaemia patients were performed allo-SCT at our centre. 20 of these 319 acute leukaemia patients relapsed after first allo-SCT and underwent second allo-SCT. 10 AML patients and 10 ALL patients were included in the study. After second allo-SCT overall survival (OS) was 26.1±10.8 weeks, and progression-free survival (PFS) was 19.9±8.6 weeks. If the patients cannot participate in clinical trials, second allo-SCT should be considered for patients with late (≥12 months) relapses after the first allo-SCT. If possible, haploidentical donors should be selected for second allo-SCT and patients should be in complete remission before the transplant.

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**1. INTRODUCTION**

Acute leukaemias are haematological malignancies characterized by abnormal proliferation of blasts caused by hematopoietic myeloid or lymphoid precursors or both. Monoclonal hematopoietic progenitor cells lose their skills to normally differentiate and proliferate. The most frequently seen acute leukaemia type in adults is acute myeloid leukaemia (AML), and it has an incidence of 5-8 /100.000.^{1,2} On the other hand, acute lymphoblastic leukaemia (ALL) has an incidence of 1.28 / 100.000, and it is less commonly observed in adults compared to AML.³ Acute leukaemias become symptomatic in a short time due to their aggressive nature. In spite of intensive treatment methods, they have a poor prognosis. Better survivals have been achieved with improvements in intensive chemotherapies and supportive care. In addition to this, targeted therapies have been started to use in selected acute leukaemia patients. Despite these improvements and new agents in acute leukaemia treatment, the relapse rate is still high.

Allogeneic stem cell transplantation (Allo-SCT) is being used as a curative treatment method in the treatment of acute leukaemia. Some patients relapse after the first allo-SCT. The acute leukaemia patients who relapse after the first allo-SCT have poor prognoses.⁴ Participating in a clinical trial is the best option for these patients. If patients cannot participate in a clinical trial, as the treatment options for these patients are limited, second allo-SCT constitutes the potential curative treatment option.⁵ Some previous studies revealed that in acute leukaemia patients who relapsed after the first allo-SCT and underwent second allo-SCT, the survival was better than those of the patients who received only chemotherapy.^{6,7,8} However, data indicate that only a limited number of acute leukaemia patients who relapsed after the first allo-SCT could be taken to the second allo-SCT.^{6,9} Because these patients previously received multiple line therapies and generally had a bad performance.^{6,9} There is still a limited number of studies regarding the efficiency of second allo-SCT and the factors impacting the survival after the second allo-SCT. The data in the literature generally come from retrospective studies conducted limited number of patients. In this study, we aimed to analyze the outcome of second allo-SCT in acute leukaemia patients who relapsed after the first allo-SCT and to find out the factors impacting the survival rates of second allo-SCT.

2. MATERIAL AND METHOD

The acute leukaemia patients who underwent the second allo-SCT due to relapsed/refractory disease after the first allo-SCT at Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Bone Marrow Transplantation Unit between December 2009 and February 2019 were included in the study. The local ethical committee approval received. Patients that underwent the second allo-SCT performed because of graft failure after the first allo-SCT was not included in the study. The data were analyzed retrospectively.

In acute leukaemia patients, complete response (CR) was described as having thrombocyte count $\geq 100.000/\mu\text{L}$, neutrophil count $\geq 1000/\mu\text{L}$ in peripheric blood, blast ratio $< 5\%$ in the bone marrow and having normal maturation in all hematopoietic series of bone marrow in addition to transfusion independence and not having the extramedullary disease.¹⁰ After achieving CR, having blasts in peripheric blood or extramedullary area or having ≥ 20 blasts in bone marrow were defined as relapse.

In both the first and second allo-SCT, peripheral blood-derived stem cells were used. Human leukocyte antigen (HLA) typing (HLA, A, B, C, DR and DQ) was performed by high-resolution method. In second transplantations, full matched (10/10) and mismatched (9/10) siblings, relatives other than siblings, unrelated donors and haploidentical related donors were used.

The intensity of conditioning regimens was classified according to the published criteria of the Center of International Blood and Marrow Transplant Research (CIBMTR).¹¹ The prophylaxis of graft-versus-host disease (GVHD) was carried out with cyclosporine. Acute GVHD was graded according to the severity index of the International Bone Marrow Transplant Registry (IBMTR).⁹ Chronic GVHD was graded according to the criteria of the National Institute of Health (NIH) 2015 consensus.¹²

The overall survival (OS) after allo-SCT was defined as the duration from transplant date to the date of death or to the date of the latest follow-up for the survivors. The progression-free survival (PFS) after allo-SCT was described as the duration from the date of the transplant to the first date when there was a progression or to the date of death or to the latest follow-up date for progression-free patients. The transplant-related mortality (TRM) was defined as the cumulative death within the first 100 days after allo-SCT without any evidence of disease progression. The engraftment definition for neutrophil was defined as the first day when the absolute neutrophil count (ANC) was $>500/\text{mm}^3$ or $1000/\text{mm}^3$ for three consecutive days without any support, and for thrombocytes, it was defined as the first day when thrombocyte count was $>20000/\text{mm}^3$ for three consecutive days without any support.¹³

The statistical analyses were performed with IBM SPSS Statistics v21 software. Chi-square test was used for descriptive statistics and comparisons among the groups for categorized data, and Mann Whitney U tests were applied for nonparametric figurative data. Survival rates were calculated by Kaplan-Meier survival analysis and Cox regression analysis. The impacts of the variables over OS and PFS were examined using a log-rank test. The cases where Type-1 error level was under 5% was accepted as statistically significant.

3. RESULTS AND DISCUSSION

Three hundred nineteen acute leukaemia patients were performed allo-SCT at our centre. Among survivors, the median follow-up is 6.4 years. TRM is %12.4. Twenty of 319 acute leukaemia patients relapsed after first allo-SCT and underwent second allo-SCT at our centre. Ten AML patients and 10 ALL patients were included in the study. There were nine female and 11 male patients. The median age at the time of the second allo-SCT was 31 (range 18-55). The median duration between first allo-SCT and relapse was 25 weeks (range 8-219 weeks). When the patients who had relapsed within 12 months after the first allo-SCT were compared with the patients who had relapsed after 12 months, PFS after the second allo-SCT was found significantly shorter in early relapsed patients ($p:0.021$); however, there was no statistically significant difference regarding OS after second allo-SCT between early and late relapsed patients ($p:0.102$).

The median duration between the first and second allo-SCT was 50 weeks (range 14-236 weeks). While we did not find any statistically significant difference between post-transplant PFS and duration between the first and second allo-SCT ($p:0.141$), we found a statistically significant difference between post-transplant OS and the duration between the first and second allo-SCT ($p:0.02^*$). Before the second allo-SCT, nine patients were full chimeric, 11 patients were mixed chimeric. In full chimeric patients, post-transplant PFS and OS were significantly longer than mixed chimeric patients ($p:0.013$).

Second allo-SCT was performed from the donors' of 10/10 compatible siblings in 11 patients, 10/10 compatible relatives other than siblings in 2 patients, 10/10 compatible unrelated in 1 patient, 9/10 compatible unrelated in 2 patients, and haploidentical donors in 4 patients.

In second allo-SCT; 13 full matched related donors (11 siblings, two relatives other than siblings), three unrelated donors (1 full matched, two mismatched), four haploidentical donors were used. In patients whose donors were related median post-transplant PFS was $21,45 \pm 9,27$ weeks and post-transplant OS was $25,42 \pm 13,34$ weeks. In patients with unrelated donors, median post-transplant PFS was only 2.5 ± 1 weeks, and post-transplant OS was three weeks. In patients with haploidentical donors, post-transplant OS and PFS were longer than patients with matched/miss-matched donors.

While in 11 patients' same donors were used in the second allo-SCT, different donors were used in 9 patients. We did not find any impacts of using alternative donors over PFS and OS. Myeloablative conditioning was used in 11 patients, and reduced intensive conditioning (RIC) regimen was used in 9 patients. There was no significant difference between post-transplant OS and PFS and conditioning regimen ($p:0.287$; $p:0.265$, respectively). The patients had an average of 1 cycle chemotherapy (range 1-3) in the duration between relapse and the second allo-SCT. While 13 patients were taken to the second allo-SCT with CR, seven patients were taken with active disease. There was no statistically significant difference between pre-transplant response and post-transplant PFS and OS ($p:0.105$ and $p:0.295$ respectively).

Median follow up duration was 34 weeks (range 20-257 weeks). 7 of 20 acute leukaemia patients (35%) performed second allo-SCT are still in remission. After second allo-SCT OS was 26.1 ± 10.8 weeks and PFS was 19.9 ± 8.6 weeks. The post-transplant PFS was 5.28 ± 2.7 weeks, and OS were 14.88 ± 8.65 weeks in AML patients while post-transplant PFS was 38.66 ± 27.6 weeks, and OS was 40.4 ± 17.1 weeks in ALL patients. There was no statistically significant difference between the patients with both diagnoses regarding the PFS and OS after second allo-SCT ($p:0.059$, $p:0.230$ respectively).

At the end of the follow-up time, nine patients died. While 3 of these deaths (15%) were related to relapse, 6 of them (30%) were related to TRM. TRM was found 20% among AML patients and 40% among ALL patients. In all patients, neutrophil engraftment occurred at a median of 14 days, and thrombocyte engraftment occurred at a median of 13 days. After the second allo-SCT, CR was observed in 9 patients (45%). Nine patients (45%) were full chimeric, 11 patients were mixed chimeric. Grade 3-4 acute GVHD was observed in 2 (10%) patients. Chronic GVHD was observed in 6 (30%) patients. The relation between post-transplant PFS and OS and diagnosis, gender, donor type, alternative donors, the presence of acute or chronic GVHD, pre-transplant response, post-transplant response, chimerism is shown in the table [\(Table 1\)](#).

Acute leukaemia patients relapsing after allo-SCT generally have received multiple line chemotherapies including various agents previously, and they usually show resistance to the previously used chemotherapeutic agents.⁴ In such patients salvage chemotherapy, discontinuation of immunosuppression, donor lymphocyte infusion, second allo-SCT can be considered. If possible, patients should be encouraged to participate in clinical trials.

In the study conducted by Cerny et al. AML, ALL, myelodysplastic syndrome and chronic lymphocytic leukaemia patients that underwent the second allo-SCT, 1-year OS was found 44%, and the median post-transplant OS was found 8.9 months (range 0-27.6 months).¹⁴ In the study conducted by Aljaseem et al., 3-year OS rate was found 35%.¹⁵ In another study, 1-year OS after second allo-SCT in AML patients was 20%.¹⁶ In an analysis of CIBMTR, 1-year OS in 369 patients that underwent second allo-SCT was 49%, and the median survival was found 12 months.¹⁷ In our study, on the other hand, the OS after the second allo-SCT was found 26.1 ± 10.8 weeks and PFS was found 19.9 ± 8.6 weeks, 1-year OS was 11%. In AML patients, the PFS after second allo-SCT was found 5.28 ± 2.7 weeks, and the OS was 10.88 ± 8.65 . In ALL patients, the PFS after second allo-SCT was found 38.66 ± 27.6 weeks and OS were found 40.4 ± 17.1 weeks.

According to the literature, CR achievement decreases as the number of chemotherapy lines increase.^{18,19} Therefore, obtaining a CR in acute leukaemia patients relapsed after the first

allo-SCT is more difficult than the second allo-SCT. In addition to this, organ functions generally impair due to high-dose treatments.¹⁹ As a result, some of the patients are taken to second allo-SCT without having a CR. Although there are many studies conducted to increase the CR rate after relapse, the results of these studies are inadequate and more studies are required.^{5,18,20,21,22} In the study conducted by Chueh et al. pre-transplant response was found to be an independent factor impacting the success of second allo-SCT.²³ In this study, 70.4% of the patients had CR before second allo-SCT. In our study, 65.2% of the patients had CR before second allo-SCT. We did not find any statistically significant difference between pre-transplant response and post-transplant PFS and OS (p:0.105 and p:0.295 respectively).

If the patients have related donors, they can use their relatives for the second allo-SCT; however, using the same donor for the second allo-SCT is relatively more difficult if the previous donors are unrelated. In the study conducted by Chueh et al., there was no difference regarding the survival rates between the patients that underwent the second allo-SCT from an alternative or the same donors.²³ In the study conducted by Aljaseem et al., no relationship was observed between OS and alternative donor use.¹⁵ The previous studies could not show the advantages of selecting an alternative donor, either.^{9,19} Similarly, we did not find any statistically significant difference between the patients that underwent second allo-SCT from the same donors or alternative donors regarding post-transplant PFS and OS.

There are studies that show the positive effects of GVHD or HLA incompatibilities on the prevention of relapse. In some studies, while positive effects are observed on the rates of survival, in other benefits could not be indicated.^{24,25,26} In the study conducted by Chueh et al., no relationship was found between acute or chronic GVHD observed after second allo-SCT and survival.²³ In our study, also, we did not find any statistically significant relationship between chronic GVHD and PFS and OS (p:0.737 and p:0.825 respectively); however, a statistically significant relationship was found between acute GVHD and PFS and OS (p:0.041 and p:0.029 respectively).

Some studies reported that the duration between the first allo-SCT and the second allo-SCT is an important prognostic factor, and it is related to better survival rates.^{27,28} In the study conducted by Chueh, there was no statistically significant survival difference between the patients with early relapses and late relapses.²³ However in the study conducted by Aljaseem et al., 3-year OS was 21% in early relapsed patients, and it was 46% in patients relapsed after 12 months (p:0.009) (20). In our study, we found shorter PFS in early relapsed patients (p:0.021), but there was no statistically significant difference regarding OS (p:0.102).

In the study conducted by Cerny et al. in second allo-SCT, median neutrophil engraftment was achieved in 15 days, and median thrombocyte engraftment was achieved in 21 days. The rate of TRM was found at 30%.¹⁴ In our study, neutrophil engraftment occurred at a median of 14 days, and thrombocyte engraftment occurred at a median of 13 days. Furthermore, the rate of TRM was similarly found 30%. The reason for early neutrophil and thrombocyte engraftment may be peripheral blood-derived stem cells.

In the majority of second allo-SCT in the literature reduced-intensity conditioning (RIC) regimens were used.²⁹ In the study conducted by Aljaseem et al., 3-year OS was found 42% in myeloablative regimens and 23% in non-myeloablative and RIC regimens; however, we did not find any statistically significant difference between myeloablative regimens and non-myeloablative and RIC regimens (p=0.08) (20). Similarly, in our study, no statistically significant relationship was found between OS and PFS and conditioning regimens (p:0.287; p:0.265).

4. CONCLUSION

Patients who were performed second allo-SCT had a poor prognosis. Development of new immune therapeutics with less toxicity and new strategies are required. Patients should be encouraged to participate in clinical trials. If the patients cannot participate in clinical trials, second

allo-transplant should be considered in patients who have late (≥ 12 months) relapses after the first allo-SCT, If possible, haploidentical donors should be selected for second allo-SCT and patients should be in CR before the transplant. More prospective studies are needed to design future treatment approaches.

DISCLOSURE STATEMENT

The authors reported no potential conflict of interest.

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Table 1. The variables that have an impact on post-transplant PFS and OS

	n	PFS after 2nd allo-SCT (weeks)	OS after 2nd allo-SCT (weeks)	P value (PFS)	P value (OS)
Gender					
Male	11	8,83 ± 3,72	14,33 ± 8,41	0,386	0,824
Female	9	31 ± 16,2	31,66 ± 30,67		
Diagnosis					
AML	10	5,28 ± 2,7	10,88 ± 8,65	0,059	0,230
ALL	10	38,66 ± 27,6	40,4 ± 17,1		
Donor Type					
Same donor	11	9,71 ± 3,44	14 ± 8,5	0,270	0,518
Alternative donor	9	32,33 ± 30,35	34,2 ± 19,38		
Donor Type					
Related donor	17	21,45 ± 9,27	25,42 ± 13,34	0,297	0,068
Unrelated donor	3	2,5 ± 1,5	3		
HLA Typing					
HLA full matched	14	17,625 ± 8,16	16,2 ± 10,06	0,034*	0,112
HLA mismatched	2	1,5 ± 1,5	1,5 ± 1,5		
Haploidentical	4	47,5 ± 43,5	48,5 ± 44,5		
Acute GVHD (grade 3-4)					
Yes	7	45,75 ± 21,195	73,5 ± 19,5	0,041*	0,029*
No	13	4,85 ± 2,58	7 ± 2,56		
Chronic GVHD					
Yes	6	31 ± 30	31,66 ± 30,67	0,737	0,824
No	14	14,33 ± 8,41	16,2 ± 7,33		
Pre-transplant Response					
CR	13	28,12 ± 12,057	28,66 ± 15,33	0,105	0,295
Refractory	7	3 ± 0,57	3,5 ± 0,64		
Relapse after 1st allo-SCT					
Early relapse	3	7,7 ± 2,6	11 ± 6,53	0,021*	0,102
Late relapse (≥12 months)	2	81 ± 10	93 ± 0		
Post-transplant Response					
CR	9	44 ± 15,44	55,66 ± 21,1	0,002*	0,018*
Refractory	11	2 ± 0,9	2,6 ± 0,92		
Chimerism					
Full	9	50 ± 18,37	55,66 ± 21,1	0,046*	0,013*
Mix	11	2,3 ± 0,66	5		

AML: acute myeloid leukemia, ALL: acute lymphoblastic leukemia, HLA: human leukocyte antigen, CR: complete response, GVHD: graft versus host disease, PFS: progression free survival, OS: overall survival

SHORT BIOGRAPHY



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He was born in Köyceğiz, Turkey. He graduated from Black Sea Technical University, Medical Faculty in 2011. Between 2012 and 2016, he worked as a Research Assistant at Internal Medicine of Mediterranean University Faculty of Medicine. He worked in Van State Hospital in 2017 as an Internal Medicine specialist. He has been working in Ankara Oncology Training and Research Hospital, Hematology Service and Bone Marrow Transplant Unit as an Hematology fellow since 2017. He has many articles published in international SCI and national journals.

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