

OUTCOME OF ALLOGENEIC STEM CELL TRANSPLANTATION WITH ACTIVE DISEASE IN ACUTE MYELOID LEUKEMIA

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Abstract: Introduction: Despite multiple lines of chemotherapy, some patients with acute myeloid leukemia (AML) can not achieve remission. The prognosis of these patients is quite poor and they should be evaluated for clinical trials, otherwise myeloablative conditioning regimens followed by allogeneic stem cell transplantation (Allo-SCT) should be performed to overcome the active disease which is resistant to conventional doses and as it is the only curative option.

Method: In this study, we evaluated the outcome of AML patients who underwent Allo-SCT with active disease in our center retrospectively.

Results: A total of 161 AML patients underwent Allo-SCT between December 2009 and November 2018 at our center. 130 of them underwent Allo-SCT in complete remission while 31 of 161 had to undergo Allo-SCT with active disease due to refractoriness to salvage therapies. The median overall survival (OS) was 7.9 ± 2.8 months. 6-month OS was 25% and 1-year OS was only 6%. Progression-free survival (PFS) was 3.53 ± 1.1 months. The transplant-related mortality rate was 12.8%.

Conclusion: OS and PFS are short in patients who undergo Allo-SCT with active disease so novel treatment approaches and targeted therapies should be developed to overcome active disease that are refractory to conventional chemotherapies.

Keywords: refractory acute myeloid leukemia, allogeneic hematopoietic stem cell transplantation, salvage therapy.

INTRODUCTION

Acute myeloid leukemia (AML) is a disease which occurs as a result of hematopoietic progenitor cells' clonal disorder that lose their skills to normally

differentiate and proliferate. In spite of intensive treatment methods, AML has poor prognosis because of its aggressive nature. Better survivals have been achieved with improvements in intensive chemotherapies and supportive care. In addition to this, targeted therapies like FMS-like tyrosine kinase 3 (FLT3) inhibitors have been started to use in selected AML cases. Despite these improvements and new agents in AML treatment, the relapse rate is still high (1, 2).

AML patients are classified into risk groups according to their genetic features and treatment plan is made according to their risk groups (3). Allogeneic stem cell transplantation (Allo-SCT) is not considered for the AML patients in good risk group in first complete remission, instead Allo-SCT should be considered in intermediate and high risk groups in first complete remission. In addition to this, in patients from all risk groups who are refractory to chemotherapy or have relapsed disease, Allo-SCT should be performed because short remission durations and high rates of relapses are expected in relapsed/refractory AML patients. In this group of patients, Allo-SCT is the only potential curative treatment option (3, 4, 5, 6)

Ideally, the patients who achieve complete remission after induction chemotherapy in intermediate and high risk groups or after salvage therapy in relapse-refractory patients should be taken to Allo-SCT. This means that patients should be in remission while they are receiving conditioning regimen before Allo-SCT. However, in spite of multiple line chemotherapy regimens, there are patients who cannot achieve remission. The prognosis of these patients is quite poor and they should be encouraged to participate in clinical trials (7, 8). If these patients cannot participate in clinical trials, myeloablative conditioning regimens followed by Allo-SCT should be performed in order to overcome the

active disease which is resistance to conventional doses and as it is the only curative option.

At this point, the main question to be answered is how we can improve the outcome of patients who have to be performed Allo-SCT while the disease is still active. Is there a way to improve overall survival similar to patients who undergo Allo-SCT while the disease is in complete remission? For this purpose we evaluated the outcome of AML patients who underwent Allo-SCT with active disease in our center retrospectively.

MATERIALS AND METHOD

A total of 161 AML patients underwent Allo-SCT between December 2009 and November 2018 at Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Bone Marrow Transplantation Center. 130 of them underwent Allo-SCT in complete remission while 31 of 161 had to undergo Allo-SCT with active disease due to refractoriness to salvage therapies. The data was collected from the clinical records retrospectively. The local ethical committee approval received.

Relaps-refractory AML patients who were over 18 years old, whose active diseases were verified by flow cytometry, immunohistochemistry analyzes, morphological findings of bone marrow aspirates and who did not have hepatic and renal failure were included in the study. The patients who did not meet criteria of participation were excluded from the study.

Complete response (CR) was defined as $< 5\%$ blast in bone marrow, absolute neutrophil count $\geq 1000 \mu\text{L}$ and thrombocyte count $\geq 100.000 \mu\text{L}$ in peripheral blood and having no blast in peripheral blood in addition to the absence of extramedullary AML. Partial response (PR) was defined as at least 50% decrease of the blast percentage after the induction chemotherapy as opposed to the initial blast percentage and having bone marrow blasts percentage between 5% and 25% (9). Disease status other than CR or PR after induction or salvage chemotherapies was described as active disease.

Overall survival (OS) was described as the duration between the first diagnosis (the date of relapse for the relapsed patients) and death or the last follow up for the survivors. OS after Allo-SCT was described as the duration between Allo-SCT and death or the last follow up for the survivors. Progression free survival (PFS) was described as the duration between the first diagnosis (the date of relapse for the relapsed patients) and progress in disease, death or the last follow up (9). PFS after Allo-SCT was described as the duration between Allo-SCT and progress in disease, death or the last follow up.

The first end point in the study was defined as OS, and the second end point was described as transplant

related mortality (TRM) and acute and chronic graft versus host disease (GVHD) incidence. The severity of acute GVHD was graded according to the grading system of International Bone Marrow Transplantation Records (IBMTR) (10). Chronic GVHD was graded according to 2015 consensus criteria of the National Institute of Health (NIH) (11).

Statistical analyses were performed by using IBM SPSS Statistics v21 software. The rates of survival was calculated by using Kaplan-Meier survival analysis. The impacts of variables on OS and PFS were studied by means of long rank test. The calculations with Type-1 error level of under 5% were accepted as statistically significant.

RESULTS

The median age of 31 patients included in our study was 37 (range 19-63). There were 24 male and 7 female patients. The patients' age, gender and distribution according to French-American-British (FAB) classification is given in Table 1. Stem cell origin (bone marrow/peripheral blood derived), donor type (related/unrelated), human leukocyte (HLA) compatibility (full matched/ mismatched/ haploidentical) and conditioning regimen used were given in Table 2.

Table 1. Clinical characteristics of the patients

Patients Characteristics	Patient	Rate (%)
Number of Patients	31	100
Gender		
Females	7/31	22,6
Males	24/31	77,4
Age		
≤ 25	6/31	19,35
26-40	14/31	45,16
≥ 41	11/31	35,49
FAB		
M0	1/31	3,22
M1	2/31	6,44
M2	4/31	12,88
M3	0/31	0
M4	4/31	12,88
M5	4/31	12,88
M6	0/31	0
M7	0/31	0
Not evaluated	16/31	51.7%

FAB: French-American-British classification

Table 2. The patients' stem cell origins, HLA compatibility, conditioning regimen and donor type

	Patient	Rate (%)
Stem Cells' Origin		
Bone Marrow	3/31	9,66
Peripheral Blood	28/31	90,34
HLA compatibility		
Full Match (10/10)	26/31	83,9
Missmatch (9/10)	3/31	9,66
Haploidentical	2/31	6,44
Donor Type		
Unrelated	2/31	6,44
Related	29/31	93,56
Conditioning Regimen		
CY-BU	18/31	58,14
CLOAMSA	6/31	19,32
BU4-FU4-ATG	7/31	22,54

CY-BU (cyclophosphamide, busulfan), CLOAMSA (clorafabine, cytarabine, amsacrine, total body radiation, cyclophosphamide), BU4-FU4-ATG (busulfan, fludarabine, Antitimositanti-globulin).

The median OS after transplantation was 7.9 ± 2.8 months. 6-month OS after transplantation was 25% and 1-year OS after transplantation was only 6%. PFS after transplantation was 3.53 ± 1.1 months. The TRM rate was 12.8%.

The evaluation of post-transplant response revealed that CR was achieved in 21 of 31 patients (71%). Relapse was observed in 10 of 31 patients (32.2%) during the first 90 days after the transplantation, in 2 patients (6.44%) between the 3rd and 12th months after Allo-SCT and in 1 patient (3.22%) in the 2nd year.

Grade III-IV acute GVHD was observed in none of the patients. Grade III-IV chronic GVHD was observed in 6.4% of patients. The variables affecting post-transplant OS in the patients who underwent Allo-SCT with active disease were age, The Eastern Cooperative Oncology Group (ECOG) performance score, Karnofsky performance score and the quantity of infu-

sed CD34⁺ stem cells. Variables affecting PFS were identified as age, the number of chemotherapy lines received, Sorrow score, the number of CD34⁺ stem cells given and the presence of GVHD (Table 3). No impact over OS was observed with gender, the number of chemotherapy lines received, blast percentage in bone marrow, the source of stem cells, European Society for Blood and Marrow Transplantation (EBMT) score, Sorrow score, the presence of GVHD, and blood type incompatibility. We did not observe any impacts of ECOG performance score, Karnofsky performance score, gender, the source of stem cells, blast percentage in bone marrow, EBMT score, blood type incompatibility on PFS. Also we did not observe significant effect of conditioning regimen over OS and PFS (p: 0.88 and p: 0.09 respectively).

DISCUSSION

Therapy options are limited in relapsed/refractory AML patients (7). This group of patients should be performed Allo-SCT, the only curative therapy method, as soon as possible as remission is achieved. Today, there are still patients who cannot achieve remission in spite of targeted therapies in addition to conventional chemotherapies (7, 8).

In our study 71% of patients achieved CR one month after Allo-SCT and the median OS after transplantation was found 7.9 ± 2.8 months. In the study conducted by Ivanoff et al., overall response rate was 38% and median OS was 9 months when refractory AML patients received 5-azasitidine maintenance followed by intensive chemotherapy. In their study, the patients who underwent Allo-SCT with active disease had higher response rate than the patients who received 5-azasitidine maintenance followed by intensive chemotherapy (66% vs 38%); however, their OS was shorter (8 months vs 9 months) (12).

In the study conducted by Mello et al., the relapse rate during the first 90 days after Allo-SCT was 56.5% in patients who underwent transplantation with active disease. TRM was 47.6% in the same study. In our study relapse was observed in 10 of 31 patients (32.2%) during the first 90 days after transplantation,

Table 3. Factors related with OS and PFS

OS	PFS
Age (p:0,002)*	Age (p:0,013)**
ECOG performance score (p:0.001)*	The number of chemotherapy lines (p:0,004)**
Karnofsky score (p:0.001)*	Sorrow score (p:0,004)**
Number of CD34+ infused (p:0,001)*	Number of CD34+ cellsinfused (p:0,002)**
	Presence of GVHD (p:0,04)**

*Factors impacting OS, **Factors impacting PFS, ECOG: Eastern Cooperative Oncology Group, GVHD: Graft versus host disease

in 2 patients (6.44%) between the 3rd and 12th months after Allo-SCT and in 1 patient (3.22%) in the 2nd year. TRM was 12.8% in our study. Although we found lower relapse and TRM rates in the first 90 days after transplantation in our study than those of the patients in the study conducted by Mello et al., PFS and OS were found to be similar (OS 7.9 months vs 8 months and PFS 3.5 months vs 3 months) (13).

In our study, cyclosporine was used for GVHD prophylaxis and the rate of grade I-II acute GVHD was 19.32%. Grade III-IV acute GVHD was not observed. The rate of grade III-IV chronic GVHD was 6.4%. In the study conducted by Mello et al. where cyclosporine and mycophenolate mofetil were used for GVHD prophylaxis, the rate of grade II-IV acute GVHD was 42.6% and the rate of grade II-IV chronic GVHD was 64.4% in the AML patients who underwent transplantation with active disease (14).

Although there was no statistically significant difference regarding post-transplant OS between the patients who had GVHD and the ones that did not present GVHD, we found that presence of GVHD had an impact on post-transplant PFS ($p:0.04$). This finding is supported with the fact that similar OS rates were found in our study and the study conducted by Mello et al., although Mello et al. observed higher GVHD rates in their study. The impact of GVHD on PFS makes us consider the importance of graft versus leukemia impact (15).

Due to acquired adverse genetic features and clonal evolution, the OS durations obtained by either repeated conventional chemotherapies or Allo-SCT is very short. Until recently, no standard therapy regimen has been identified for the relapse/refractory AML patients as a salvage therapy. Reaching to the newly developed targeted therapies such as FLT-3 inhibitors, isocitrate dehydrogenase (IDH) inhibitors according to the genetic risk features prior to the transplantation will also be reflected on the results of transplantation.

In conclusion; OS and PFS are short in patients who undergo Allo-SCT with active disease so new treatment approaches and targeted therapies should be developed in order to overcome active diseases which are refractory to conventional chemotherapies. Therefore, such patients should be supported to participate in clinical trials as much as possible. There are a number of ongoing clinical trials for the development of new therapy methods (14, 16, 17). In addition to this, Allo-SCT is still a valid therapy option in relapsed/refractory patients that are unable to reach clinical trials but new therapy approaches that would reduce TRM, relapse rates and GVHD incidence in AML patients that are admitted to transplantation with active disease are required.

Abbreviations

EBMT — European Society for Blood and Marrow Transplantation

ECOG — Eastern Cooperative Oncology Group

FAB — French-American-British

GVHD — graft versus host disease

TRM — transplant related mortality

AML — acute myeloid leukemia

Allo-SCT — allogeneic stem cell transplantation

OS — overall survival

PFS — Progression-free survival

CR — Complete response

PR — Partial response

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Sažetak

ISHOD ALOGENE STEM ĆELIJSKE TRANSPLANTACIJE SA AKTIVNOM BOLEŠĆU KOD AKUTNE MIJELOIDNE LEUKEMIJE

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Uvod: Uprkos mnogim linijama hemoterapije, neki pacijenti sa akutnom mijeloidnom leukemijom (AML) ne mogu da postignu remisiju. Prognoza ovih pacijenata je izuzetno loša i trebalo bi ih istražiti u kliničkim studijama, jer se u protivnom moraju sprovesti

mijeloablativni režimi kondicioniranja praćeni alogenom ćelijskom transplantacijom matičnih ćelija (Allo-SCT) da bi došlo do aktivne bolesti i koja je rezistentna na uobičajene doze i kao takva je jedina terapija izbora.

Metod: U ovoj studiji smo evaluirali ishod pacijenata sa AML koji su retrospektivno podvrgnuti Allo SCT sa aktivnom bolešću u našem centru.

Rezultati: Ukupno 161 pacijent sa AML je podvrgnut Allo-SCT između decembra 2009. te i novembra 2018. te godine u našem centru: 130 njih podvrgnuto je Allo SCT u potpunoj remisiji, dok je 31 od 161 morao da se podvrgne aktivnoj bolesti Allo SCT zbog otpornosti na terapije. Medijana ukupnog preživljavanja bila je $7,9 \pm 2,8$ meseci. 6-mesečno preživljavanje bilo je zabeleženo kod 25% a jednogodišnje preživljanje

kod samo 6%. Preživljavanje bez progresije (PFS) bilo je $3,53 \pm 1,1$ meseci. Transplant-related stopa mortaliteta bila je 12.8%.

Zaključak: OS i PFS su kratki kod pacijenta koji su podvrgnuti Allo SCT sa aktivnim bolestima. Takođe teballo bi da se razviju terapije koje bi bile specifične kako bi se prevazišlo aktivno stanje bolesti, koje su refraktorne na konvencionalne hemoterapije.

Ključne reči: refraktorna akutna mijeloidna leukemija, alogena hematopoetska stem ćelijska transplantacija, terapija spasa.

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