Original Article

How are the Results of Allogeneic Stem Cell Transplantation in Elderly Patients? A Single-Center Experience

Yaşlı Hastalarda Allojeneik Kök Hücre Nakli Sonuçları Nasıl? Tek Merkez Deneyimi

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ABSTRACT

Aim: In this study, we aimed to present allogeneic hematopoietic stem cell transplantation (allo-HSCT) experience in elderly patients with hematological malignancy.

Materials and methods: Thirty-five patients aged 60 years and older who underwent allo-HSCT between 2017 and 2021 were retrospectively analyzed. Patient's demographic/clinical features, and the outcomes of transplantation were reviewed.

Results: The median age was 63 (range, 60-74) years and 25 (77,1%) were male. Twenty-seven (60%) were diagnosed with AML, followed by MDS (n:7, 20%). Twenty-three (65,8%) patients had intermediate, and 6 (17,1%) patients had a high hematopoietic cell transplantation-specific comorbidity index score. Karnofsky performance status of ≥ 90% was detected in 15 (42,9%) patients. Busulfan plus fludarabine plus anti-thymocyte globulin was used mainly as a reduced-intensity conditioning regimen, which was used in 18 (51,4%) patients. The median duration of neutrophil and platelet engraftments were 18 (range, 11-27) and 18 (range, 11-33) days, respectively. The median follow-up time was 4 months (range, 0-51), with the OS rate %14,2. The transplant-related mortality rate within the first 30 days after allo-HSCT was detected in 10 patients (28,6%) due to infection and/or GvHD. Response assessment could be performed in 25 (71,4%) patients after transplantation. The duration of PFS was 6 (range, 1-51) months in patients with response evaluation. The rate of PFS was 72% in 1 years and 5 (14,2%) patients were still alive with complete response at the last visit.

Conclusion: Reduced-intensity conditioning regimen has provided the advantage in allo-HSCT, for elderly patients with hematological malignancies such as AML and MDS.

Keywords: allogeneic hematopoietic stem cell transplantation, elderly patients, reduced-intensity conditioning regimen

ÖZET

Amaç: Biz bu çalışmada 60 yaş ve üzerindeki hematolojik malignitesi olan hastalarda allo-HSCT deneyimini ve sonuçlarını sunmayı amaçladık.

Gereç ve yöntemler: 2017-2021 yılları arasında allo-HSCT uygulanan 60 yaş ve üstü 35 hasta retrospektif olarak analiz edildi. Hastaların nakil anındaki demografik ve klinik özellikleri ile nakil sonuçları incelendi.

Bulgular: Ortanca yaş 63 (60-74) ve 25'i (%77,1) erkekti. Yirmi yedi (%60) hasta AML, 20 (%20) hasta MDS tanılıydı. Yirmi üç (%65,8) hastada orta, altı (%17,1)' sında yüksek hematopoietik hücre transplantasyonu spesifik komorbidite indeks skoru vardı. 15 (%42,9) hastada Karnofsky performans durumu ≥%90 olarak saptandı. Busulfan, fludarabin ve anti-timosit globulin kombinasyonu en sık kullanılan RIC rejimiydi ve 18 (%51,4) hastada kullanıldı. Ortanca nötrofil ve trombosit engraftman süresi sırasıyla 18 (11-27) ve 18 (11-33) gündü. Ortanca takip süresi 4 aydı (aralık, 0-51), toplam sağkalım oranı %14,2. Allo-HSCT' den sonraki ilk 30 gün içinde transplanta bağlı ölüm oranı enfeksiyon ve/veya GvHD nedeniyle 10 hastada (%28,6) tespit edildi. Nakil sonrası 25 (%71,4) hastada yanıt değerlendirmesi yapılabildi. Yanıt değerlendirmesi yapılan hastalarda PFS süresi 6 (dağılım, 1-51) aydı. PFS oranı 12 ayda %72 idi. Son kontrolde 5 (%14,2) hasta tam yanıtla halen yaşıyordu.

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Sonuç: Azaltılmış yoğunluklu şartlandırma rejimi, özellikle AML ve MDS gibi hematolojik maligniteleri olan yaşlı hastalarda allo-HSCT' de önemli bir avantaj sağlamıştır.

Anahtar Kelimeler: allojeneik hematopoietik kök hücre nakli, yaşlı hastalar, düşük yoğunluklu hazırlama rejimi

Introduction

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is the important treatment option for many hematological malignancies and benign hematological disorders [1]. However, complications such as post-transplant infection and graft versus host disease (GvHD) increase the rate of transplant-related mortality (TRM) and morbidity [2]. In the literature, high TRM (50%) rates have been reported [3]. Furthermore, many hematological malign diseases significantly affect the elderly. The median age at diagnosis is over 60 years in disease such as acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS)in which allo-HSCT is very important [4-6]. Therefore, allo-HSCT as a salvage or consolidation treatment option could be used limitedly as a treatment option in elderly patients with multiple comorbidities [7].

The performance status and comorbidity are other factors determining the eligible transplant candidate and affecting the transplant outcome [8]. Hematopoietic cell transplantation-specific comorbidity index (HCT-CI) is used widely before the transplantation for transplant-risk assessment. Patients are stratified into 3 (score 0, 1–2, or ≥3) categories according to the HCT-CI. The TRM rate is found to be high in those with a score of 3 and above. [9]. Karnofsky performance score (KPS) is determined by evaluating functional abilities to perform routine daily activities. Generally, KPS below 60-70% is considered an exclusion factor for transplantation [8, 10].

Myeloablative conditioning regimen (MAC) could not be used in elderly and frail patients due to the significant risk of adverse effect. However, a reduced-intensity conditioning (RIC) regimen has shown significant benefits in TRM and morbidity [11-13]. In addition, TRM rates were reduced with the determination of the eligible transplant candidate, the development of GvHD prophylaxis, and the improvement in post-transplant supportive and infection therapy[4, 5, 14].

In this study, it was aimed to review allo-HSCT experience and outcomes in elderly patients who were 60 years old and older with hematological malignancy disorders.

Materials and Methods

We retrospectively analyzed 35 patients who were 60 years and older and underwent allo-HSCT between 2017 and 2021. The age, gender, performance score, comorbidity, disease status at the transplantation, number of treatment lines before the transplantation, donor type, the conditioning regimen, the quantity of CD34+ stem cells infused, the duration of neutrophil/platelet engraftment, the presence of febrile neutropenia/acute-chronic graft versus host disease, TRM, and duration of hospitalization, progression-free survival (PFS) and overall survival (OS) were examined. All data were collected from the hospitals' registries and patients' clinical notes.

Performance status was evaluated with KPS, and comorbidity status was evaluated with HCT-CI. The HCT-CI were each separated into 3 risk groups low (0), intermediate (1-2), and high (≥ 3) risk [9, 10].

Neutrophil engraftment duration was defined as the time from the first day of allo-HSCT to

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the first of three consecutive days with absolute neutrophil counts $\geq 0.5\times10^9$/L. Platelet engraftment duration was defined as the time from the first day of allo-HSCT to the first of three consecutive days with platelet counts of more than 20×10^9/L without transfusion. Febrile neutropenia was defined as the combination of granulocyte counts below 500 cells/µl and temperature over 38 oC. Acute GvHD was evaluated according to the revised Glucksberg scale. Chronic GvHD was diagnosed and staged according to the National Institutes of Health (NIH) Consensus Criteria[15, 16].

Transplant-related mortality was defined as death within the first 30 days after allo-HSCT without any evidence of disease relapse or progression. Progression-free survival was defined as the time from initiation of transplantation to the occurrence of disease relapse or death. Overall survival was defined from the first day of allo-HSCT to death from any cause.

This study was conducted with approval by the Ethics Committee of Inonu University with approval number 2021/2875 and was carried out by the principles of the Helsinki Declaration.

Statistical analysis

Numbers and percentages were used for categorical data in descriptive analyses. Continuous data were classified as parametric and non-parametric with skewness–kurtosis, Kolmogorov–Smirnov test, standard deviation/mean percentages, and histogram graphics with regular distribution lines. For parametric and non-parametric data, mean±standard deviation and median(min-max) values were used, respectively. For univariate analysis overall survival was calculated by Kaplan-Meier method and log-rank test was performed. Cox regression analysis was performed to determine significant predictors of age and the dose of CD34+ stem cells variables. Values of $p<0.05$ were accepted as statistically significant. All data analyzes were performed using Statistical Package for Social Sciences (SPSS) version 22.0 (Armonk, NY: IBM Corp.).

Results

Twenty-five (77,1%) of them were male. The median age at the time of transplantation was 63 (range, 60-74) years, and only two (5,7%) patients were older than 70 years old. Thirty-one (n:27, 60%) were diagnosed with AML, followed by MDS (n:7, 20%). Thirteen (48,1%) of 27 patients with AML had a complete response (CR) at the time of allo-HSCT. Twenty-three (65,8%) patients had intermediate, and six (17,1%) patients had a high hematopoietic cell transplantation-specific comorbidity index (HCT-CI) score. The comorbidities were pulmonary dysfunction (17,1%), cardiac disease (14,2%), infection (14,2%), diabetes mellitus (11,4%), psychiatric disturbance (5,7%), arrhythmia (2,8%), cerebrovascular disease (2,8%), and rheumatologic disease (2,8%). Karnofsky performance status of ≥90% was detected in 15 (42,9%) patients. The demographic and clinical characteristics of the patients were presented in Table 1.

The median time from diagnosis to allo-HSCT was three (1-75) months. The HLA-matched sibling donor (MSD) was used most frequently as the donor type, which was used in 28 (80%) patients. A reduced conditioning regimen was used most frequently as the conditioning regimen, which was used in 31 (88,6%) patients. Busulfan plus fludarabine plus anti-thymocyte globulin (ATG) regimen was primarily used as a reduced-intensity regimen, which was used in 18 (51,4%) patients. Treosulfan plus fludarabine plus ATG therapy and fludarabine plus amsacrine plus cytarabine (FLAMSA) therapy were the other RIC regimens were used in nine (25,7%) and four (11,4%) patients, respectively. Busulfan plus cyclophosphamide was used as the MAC regimen, which was used in only

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Table 1. The demographic and clinical characteristics of the patients at the time of transplantation

	N:35
Median age (range)	63 (60-74)
Gender, n (%)	
Male	27 (77,1)
Female	8 (22,9)
Disease type, n (%)	
AML	21 (60)
MDS	7 (20)
ALL	2 (5,7)
PMF	2 (5,7)
Others	3 (8,6)
Disease status, n (%)	
CR	18 (51,4)
PR	6 (17,1)
Refractory	11 (31,4)
The median time from diagnosis to transplant, (range), months	3 (1-75)
The median prior therapy line, (range)	1 (0-3)
Karnofsky performance score, n (%)	
≥90	15 (42,9)
<90	20 (57,1)
HCT-CI, n (%)	
Low	6 (17,1)
Intermedia	23 (65,8)
High	6 (17,1)
LDH, n (%)	
Normal	13 (37,1)
High	22 (62,9)
CRP, n (%)	
Normal	29 (82,9)
High	6 (19,1)
Cytomegalovirus serologic status, n (%)	
Positive	34 (97,1)
Negative	1 (2,9)

ASCT; autologous stem cell transplantation, AML; acute myeloid leukemia, ALL; acute lymphoblastic leukemia, CR; complete response CRP; C-reactive protein, HCT-CI; hematopoietic cell transplantation-specific comorbidity index, LDH; lactate dehydrogenase, MDS; myelodysplastic syndrome PMF; primary myelofibrosis, PR; partial response

four (11,4%) patients. Cyclosporine A plus methotrexate combination was used in all patients due to GvHD prophylaxis.

The stem cell source was peripheral blood in all patients. The median counts of infused stem cells were $8,1x10^6$/kg (range, 5,1-$19,4x10^6$/kg). The median duration of neutrophil engraftment and platelet engraftment were 18 (range, 11-27) and 18 (range, 11-33) days, respectively. The neutrophil and platelet engraftments did not occur in 11 (11,4%) and 11 (11,4%) patients, respectively. Febrile neutropenia was detected in 25 (71,4%) patients. The median time of hospitalization was 19 (range, 1-50) days. Transplantation characteristics and post-transplantation outcomes were shown in Table 2.

Table 2. Peritransplantation features and outcome of transplantation

	N: 35
Donor type, n (%)	
Matched related	28 (80)
Matched unrelated	5 (14,3)
Haploidentical	2 (5,7)
Conditioning regimen n (%)	
Myeloablative	4 (11,4)
Reduced induced	31 (88,6)
The median count of infused CD34+stem cell $\times10^6$/kg (range)	8,1 (5,1-19,4)
The median time to neutrophil engraftment (range), day	18 (11-27)
The median time to platelet engraftment (range), day	18 (11-33)
The rates of febrile neutrophile, n (%)	
Yes	25 (71,4)
No	10 (28,6)
The median duration of hospitalization (range), day	19 (1-50)
Transplant-related mortality, n (%)	
Yes	15 (42,8)
No	20 (57,2)
Disease status after transplantation	
CR	18 (51,4)
PR	2 (5,7)
Refractory/relaps	5 (14,3)
Not detectable	10 (28,6)
Acute GvHD status, n (%)	
Yes	10 (28,6)
Chronic GvHD status, n (%)	
Yes	3 (8,3)

CR; complete response, GvHD; graft versus host disease, PR; partial response

The median follow-up time was 4 months (range, 0-51), with the OS rate %14,2. The median OS was 4 months (95% CI: 2,1-5,8). The transplant-related mortality rate within the first 30 days after allo-HSCT was detected in 10 patients (28,6%) due to infection and/or GvHD. The age at the time of transplantation, gender, HCT-CI score, Karnofsky performance status, disease status at time of transplantation, the conditioning regimen, and

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Table 3. The univariate analyses for overall survival

Variables	Median overall survival (months)	95% CI	p valuable
Gender			
Male	4,00	2,31-5,69	.889
Female	1,00	0-4,70	
Age*	0,969	0,842-1,115	.658
HCT-CI			
Score 0	4,00	0,60-7,40	
Score 1-2	4,00	2,45-5,55	.820
Score ≥3	1,00	0-3,40	
Karnofsky performance score			
<90%	4,00	0,21-7,79	.273
≥90%	2,00	0-6,38	
Disease status at the time of allo-HSCT			
Complete and partial response	4,00	0-8,78	.215
Refractory/progression	3,00	0-7,16	
The conditioning regimen			
Myeloablative	4,00	0-9,88	.424
Reduced induced	4,00	1,34-6,66	
The dose of CD 34 stem cell dose*	1,072	0,951-1,210	.254

HCT-CI; hematopoietic cell transplant comorbidity index, allo-HSCT; allogeneic hematopoietic stem cell transplantation
*Hazard ratio (95% confidence interval)

the dose of infused CD34+ stem cells were not statistically significantly associated with OS (Table 3).

Response assessment could be performed in 25 (71,4%) patients after transplantation. Ten (28,6%) patients died before a response assessment could be performed. The rate of PFS was 72% in 12 months. At the last follow-up, five (14,2%) patients were still alive with CR. Only three (10%) deaths were related to relapse/progressed disease.

Acute GvHD occurred in 10 (28,6%) patients as only gastrointestinal acute GvHD in four(11,4%) patients, only skin acute GvHD in five(14,2%) patients, and both gastrointestinal and liver acute GvHD in one (2,8%) patient. Grades III/IV acute GvHD occurred in six (17,1%) patients. Chronic GvHD occurred in three (8,3%) patients (one limited and two extended) surviving more than 100 days after allo-HSCT.

Discussion

Allo-HSCT can be used limitedly as a treatment option in elderly patients with comorbidities. However, in recent years, it has been more preferred in elderly patients due to the improvement of the conditioning regimens, the determination of prognostic factors before transplantation, and the improvement in post-transplant supportive treatments. In this retrospective study, 35 patients older than 60 years were evaluated who underwent allo-HSCT.

Comorbidity and performance status are the determining factors in selecting eligible patients in allo-HSCT. Sorror et al. presented the impact of HCT-CI and KPS on NMA allo-HCST outcomes and emphasized that both HCT-CI 3 and above scores and KPS percentages 80% or less were found to be important predictor of grade 3-4 toxicities and higher mortality (HCT-CI score: p=0.004, p=0.0002 and KPS: p=0.05, p=0.002, respectively). Furthermore, high HCT-CI scores were statistically significantly associated with increased NRM (p=0.0002) [17]. Other studies demonstrated that the HCT-CI score was a significant prognostic impact on OS (2-year OS, 58%, 53%, and 43% for scores 0, 1-2, and ≥3, respectively, p =0.004)[18]. In our study, 6 (17,1%) patients had low HCT-CI scores, 23 (65,8%) patients had intermediate HCT-CI scores, and six (17,1%) patients had high HCT-CI scores, whereas 20 (57,1%) patients had a KPS of

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<90%. However, the comorbidity and KPS status in terms of overall survival could not be compared as they were small and heterogeneous groups.

Non-myeloablative (NMA) or RIC regimens are often preferred over myeloablative regimens to reduce toxicity for elderly patients in allo-HSCT. Wallen et al. presented the results of allo-HSCT with myeloablative regimens in adults 60 years of age and older. They evaluated 52 patients with a median age of 62.8 years who underwent allo-HSCT with MAC regimens. In their study, TRM rates at 100 days and 3 years are 27% and 43%, respectively. Grade ≥3 GVHD and extensive chronic GVHD occurred 20% and 53%, respectively [19]. However, the outcomes of allo-HSCT in elderly patients (median age, 69 years; range, 66-77) who underwent allo-HSCT using the RIC regimen were presented by Hsu et al. Most patients (85%) had received fludarabine/melphalan-based RIC regimen. The incidence of TRM mortality was 11,5% at 100 days. The grades II to IV GVHD at day 100 and 6 months was 29,5% and 34,5%, and chronic GVHD at 6, 12, and 24 months was 2.5%, 5.2%, and 6.3%, respectively[5]. In our study, the RIC regimen was used in 31 (88,6%) patients, and TRM was detected in 10 patients (28,6%) within the first 30 days after allo-HSCT. Acute GvHD occurred in 10 (28,6%) patients. Grades III/IV acute GvHD occurred in six (17,1%) patients. Chronic GvHD occurred in three (8,3%) patients. Although our TRM rates were higher than the literature, the outcome of both acute and chronic GVHD rates were similar with the literature. We attribute this to the frail of our cohort because most of them (57,1%) had KPS below 90% and majority of them (82,9%) had moderate and high HCT-CI score.

Although TRM is low with RIC regimens, the risk of relapse is more than with myeloablative therapies, as a disadvantage. Scott et al. presented the long-term follow-up of the study that MAC compared with RIC for AML and MDS. They reported that the risk of relapse was high in the RIC regimen compared to the received MAC (hazard ratio, 4.06; 95% CI, 2.59 to 6.35; p <0.001) [11]. Acute Leukemia Working Party of the European Group for Blood and Marrow Transplantation presented the comparative outcome of RIC and MAC regimen in HLA identical sibling allo-HSCT for patients older than 50 years with AML. They reported that the relapse rate was statistically significantly higher in the RIC group (RIC: 41% vs. MAC: 24%, p<0.0001) [20]. However, a phase 3 study compared the treosulfan-based conditioning regimen with the busulfan-based conditioning regimen in older patients with AML or MDS. The relapse or progression rates were detected at 20% and 21%, respectively. There was no significant difference between the two groups regarding recurrence or progression (p=0,50) [21]. In our study, the rate of PFS was 72%, and the progression rate was 14,3% in 12 months. Busulfan plus fludarabine or treosulfan plus fludarabine were used mainly as the conditioning regimen in our study, and our relapse rates were consistent with this phase 3 study.

In the RIC regimen, fludarabine is combined with an alkaline agent such as melphalan, busulfan, treosulfan, and thiotepa or with total body irradiation (TBI). The dose of alkylating agents or TBI is reduced in the RIC regimens, and thus the duration of cytopenia is shortened compared to MAC regimens[22, 23]. A study about the outcome of older patients who underwent allo-HSCT using RIC regimens reported the median time to neutrophil and platelet engraftment were 13 days (range, 8 to 37) and 17 days, respectively[5]. In a randomized and phase 3 trial, treosulfan plus fludarabine was compared with busulfan plus fludarabine for older patients with AML or MDS who underwent allo-HSCT. At day 28 after HSCT, neutrophil engraftment was

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achieved 96.8% in treosulfan-treated patients and 96.2% in busulfan-treated patients (p=0.34). Platelet engraftment was achieved in 97% and 98% of patients, respectively (p=0.077)[21]. In our study, busulfan and treosulfan-based conditioning regimens were mainly used (51,7%vs.25,7%, respectively). The median time of neutrophil engraftment and platelet engraftments were 18 (range, 11-27) and 18 (range, 11-33) days, respectively. The neutrophil and platelet engraftments did not occur in 11 (11,4%) and 11 (11,4%) patients, respectively. The duration of engraftment was consistent with the literature, but our engraftment rates were lower than the literature. This difference was thought to be due to infection-related deaths in the early transplant period (first 30 days after allo-HSCT).

The small and heterogeneous population was the most significant limitation of our study. Therefore, subgroup and comparison analyses were not performed. Another limitation was that it was a retrospective study.

In conclusion, RIC and NMA regimens provide a significant advantage for patients with advanced age with hematological malignancies such as AML and MDS, which have an essential role in the treatment of allogeneic transplantation. However, comorbidities and transplant-related mortality such as GVHD or infection still pose a significant transplant disadvantage for allo-HSCT in elderly and frail patients

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