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ORIGINAL ARTICLE

Long-Term Outcomes of Allogeneic Stem Cell Transplantation for Relapsed/Refractory Hodgkin and Non-Hodgkin Lymphoma: Multi-center Experience from Turkey

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Abstract This multicenter retrospective study evaluated the efficacy of allogeneic hematopoietic stem cell transplantation (allo-HSCT) on survival and safety in patients with relapsed/refractory (R/R) Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). A total of 110 patients with R/R HL or NHL who underwent allo-HSCT between July 2007 and October 2022 at 7 adult stem cell transplant centers were evaluated. Progression-free survival (PFS), graft versus host disease-free survival (GRFS), and overall survival (OS) were the primary endpoints, and NRM was the secondary endpoint. Forty-one (37.3%) of the total patients were diagnosed with HL, 69 (62.7%) with NHL. The median age at the time of allo-HCT was 39.5 years (16–67), of which 66 (60%) were male. The median follow-up was 67.5 ± 8.1 months, and the rates of 5-year OS, PFS, and GRFS were 38.4%, 37%, and 34.8%, respectively. On multivariate analysis, CR/PR disease status after allo-HCT was significantly associated with longer PFS (HR: 13.47, 95% CI: 5.80–31.26, $p = 0.000$) and OS (HR: 5.23, 95% CI: 2.93–9.34, $p = 0.000$). CR/PR disease status after allo-HCT (HR: 5.79, 95% CI: 3.22–10.40, $p = 0.000$) and grade 1–2 acute GvHD (HR: 2.33, 95% CI: 1.25–4.35, $p = 0.008$) were significantly associated with longer GRFS. The 5-year cumulative incidence of NRM was 24.8% (95% CI, 12.5–36.7). The most common conditioning regimen was reduced intensity. Transplant outcomes are not influenced by disease subtype. However, the achievement of a CR/PR response after allo-HCT significantly prolongs OS, PFS and GRFS. In addition, the presence of acute grade 1–2 GvHD was found to be another factor prolonging GRFS. These results support the feasibility of allo-HCT, especially in heavily treated patients.

Keywords Allogeneic hematopoietic stem cell transplantation · Graft versus host disease-free relapse-free survival · Lymphoma · Progression-free survival · Overall survival

Abbreviations

CMV	Cytomegalovirus
GVHD	Graft-versus-host disease
VOD/SOS	Veno-occlusive disease/sinusoidal obstruction syndrome

Introduction

Lymphomas are the most common hematologic malignancies and consist of a heterogeneous group of diseases including Hodgkin's lymphoma (HL) and non-Hodgkin's lymphoma (NHL) [1, 2]. NHL is the more common subtype,

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accounting for nearly 85–90% of lymphomas, and is divided into 2 subtypes, including B-cell NHL and T-cell NHL. Approximately 20–30% of NHL patients relapse after initial remission or become resistant to first-line chemotherapy [3–5]. HL is a rarer subtype that accounts for 10–15% of lymphomas and is a highly curable disease, especially in early stage disease, with a cure rate of 85% and above after initial therapy. However, the rate of relapse/refractory (R/R) disease after initial treatment is 10–15% in HL [6–8]. In recent years, especially in the last decade, there have been important developments in the treatment of both HL and NHL. New targeted therapies such as monoclonal antibodies, immune check point inhibitors, Bruton's tyrosine kinase inhibitors, phosphoinositide 3-kinase inhibitors have significantly improved the outcome of R/R lymphoma. In particular, the 5-year overall survival (OS) rate in NHL has reached over 70% [1–3, 9].

Despite advances in the treatment of both HL and NHL in recent years, R/R lymphoma remains an important problem associated with poor prognosis in patients with lymphoma [6, 10]. Progression or relapse after autologous hematopoietic cell transplantation (auto-HCT) has a poor outcome in both HL and NHL [11, 12]. Allogeneic hematopoietic stem cell transplantation (allo-HCT) remains the only curative treatment option for patients with R/R disease. Allo-HCT is generally an optional treatment choice for young and fit patients with R/R lymphoma who have been heavily pretreated and after failure of auto-HCT [10]. In contrast to auto-HCT, allo-HCT offers patients in this low-risk group the benefit of the graft-versus-lymphoma effect and thus has a positive impact on improving survival outcomes. In a study comparing the results of allo-HCT and auto-HCT transplantation, the relapse rate after allo-HCT was lower than after auto-HCT (6% vs. 41%, respectively) [12–14]. In recent years, allo-HCT has been used more intensively in lymphoma patients, and the use of reduced-intensity conditioning (RIC) and non-myeloablative (NMA) regimens has been shown to reduce transplant-related and relapse-related mortality and provide favorable long-term survival.[15, 16].

In this retrospective multicenter study, we aimed to evaluate the efficacy and safety of allo-HCT on survival in patients with R/R lymphoma.

Materials and Methods

Patients

We evaluated 110 patients with R/R HL or NHL lymphoma who underwent allo-HCT between July 2007 and October 2022 in 7 adult stem cell transplantation centers from Turkey.

Patient information was obtained from the hospital registry system. Patient demographic and clinical characteristics, performance score, pretransplant treatments, donor type, disease status at time of transplantation, conditioning regimen, infused CD34+ stem cell dose ($\times 10^6$/kg), Graft-versus-Host Disease (GvHD) prophylaxis, transplant outcomes, and survival were evaluated.

Performance status was assessed using the Karnofsky Performance Score (KPS). Response was classified as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) according to the Lugano revised response criteria [17]. The overall response rate (ORR) was defined as the sum of CR and PR rates. Acute GvHD was graded according to the revised Glucksberg scale. Chronic GvHD was diagnosed and staged according to the National Institutes of Health (NIH) consensus criteria [18, 19]. The Baltimore criterion was used to diagnose veno-occlusive disease-sinusoidal obstruction syndrome (VOD/SOS) [20].

The primary endpoints of this study were progression-free survival (PFS), GvHD-free, relapse-free survival (GRFS) and OS after allo-HCT. The secondary endpoint was non-relapse mortality (NRM).

This study was approved by the Ethics Committee of Ege University (approval number: 21-8T/55) and conducted in accordance with the tenets of the Declaration of Helsinki.

Donor Type

Human leukocyte antigen (HLA) typing (HLA-A, HLA-B, HLA-C, HLA-DRB1, and HLA-DQB1 by high-resolution typing method) was used for donor selection. Donors were defined as follows: matched related donor (MRD) and matched unrelated donor (MUD), mismatched unrelated donor (MMUD) where HLA compatibility was 9/10 or 8/10, and haploidentical donor where HLA compatibility was 7/10 and below.

Conditioning Regimens

Conditioning regimens were selected according to the experience and guidelines of the centers, which were classified as RIC and myeloablative conditioning (MAC) according to established criteria [21].

Prophylactic Therapy

Treatment choices for GvHD prophylaxis were determined according to center experience. Defibrotide monotherapy, heparin monotherapy, defibrotide plus heparin, and ursodeoxycholic acid (UDCA) monotherapy were used for VOD/SOS prophylaxis. According to Turkish reimbursement conditions, defibrotide is used for VOD/SOS prophylaxis in

patients with at least one of the following conditions: previous radiotherapy, pre-existing liver disease, iron overload, HBV or HCV infection, unrelated donor transplantation, busulfan-containing regimens, and previous transplantation with MAC conditioning regimen. High risk was defined by the treating physician according to reimbursement conditions and patient characteristics (age > 60 years, poor performance status (Karnofsky score < 90%)). Antibacterial, antiviral, antifungal, and prophylactic agents were used according to the guidelines of each transplant center.

Definitions

Neutrophil engraftment time was defined as the time from the day of stem cell infusion to the first of three consecutive days with absolute neutrophil counts $\geq 0.5 \times 10^9$/L. Platelet engraftment time was defined as the time from the day of stem cell infusion to the first of three consecutive days with platelet counts $> 20 \times 10^9$/L without transfusion. Complete donor chimerism was defined as > 95–100% donor origin of hematopoietic cells. Mixed donor chimerism was defined as the presence of both donor and recipient hematopoietic cells [22]. Primary and secondary graft failure were defined according to the literature [23].

Non-relapse mortality (NRM) was defined as death after allo-HCT without evidence of disease relapse or progression. PFS was calculated from the first date of allo-HCT to the date of relapse/progression or death. GRFS was defined as survival without grade III–IV acute GvHD or chronic GvHD without systemic immunosuppression, relapse or death. OS was calculated from the date of the first day of allo-HCT to death from any cause or last follow-up.

Statistical Analysis

Variables were first tested for normal distribution using Kolmogorov–Smirnov/Shapiro–Wilk tests. Results were presented as mean ± standard deviation for normally distributed variables and as median (minimum–maximum) for abnormally distributed parameters. Associations between clinical parameters and survival were evaluated using Cox univariate and multivariate analyses. All p values were two-tailed, and statistical significance was set at the level of $p < 0.05$. Survival analysis was performed using the log-rank test and Kaplan–Meier curves. Statistical analyses were performed using SPSS 18 (SPSS Inc., Chicago, IL, USA).

Results

Patients and Transplant Characteristics

Forty-one (37.3%) of 110 patients were diagnosed with HL, 69 (62.7%) with NHL. The median age at transplantation was 39.5 years (16–67) and 66 (60%) were male. HCT-CI was 0 in 43 patients, 1 in 16 patients and 2 in 5 patients. HCT-CI data were not available for 46 patients. Eight (7.3%) patients were treated with nivolumab, of which 3 (37.5%) were diagnosed with NHL and the rest (n = 5, 62.5%) with HL. The most commonly used conditioning regimen was the RIC regimen (n: 81, 73.6%). The most common RIC regimen was busulfan plus fludarabin with or without anti-thymocyte globulin (ATG) (n: 36, 45.1%). The most common MAC regimen was busulfan plus fludarabin (n:6, 20.7%), followed by busulfan plus cyclophosphamide (n:5, 17.2%). GvHD prophylaxis was used in all but 2 patients (1.8%). The most commonly used GvHD prophylaxis was cyclosporine plus methotrexate (n:70, 64.8%), followed by cyclosporine monotherapy (n:11, 10.1%). ATG-based GvHD prophylaxis was used in only 3 patients (2.8%). GvHD prophylaxis was not used in 2 patients, one of whom underwent haploidentical allo-HCT with T-cell depletion of bone marrow-derived stem cells using the MAC regimen. The other patient underwent allo-HCT with peripheral blood stem cells from a syngeneic MRD donor using the RIC regimen. VOD/SOS prophylaxis was used in 61 (55.5%) patients. Defibrotide monotherapy and heparin monotherapy were mainly used for VOD/SOS prophylaxis in 38 (34.5%) and 11 (10%) patients, respectively. The other prophylactic treatments were defibrotide plus heparin and UDCA monotherapy, which were used in 9 (8.2%) and 3 (2.7%) patients, respectively. The demographic, clinical, and transplant characteristics of the patients at the time of transplantation are shown in Table 1.

Transplant Outcomes

Transplant outcomes are shown in Table 2. The ORR was 79 (71.8%) patients. Long-term survival was achieved in 7 of 32 (21.9%) patients who were initially chemo-refractory. The median follow-up of these patients was 82 months (23–164).

Neutrophil and platelet engraftment failed in 8 (7.3%) and 12 (10.9%) patients, respectively. Two patients without neutrophil engraftment did not survive to engraftment. Six patients experienced primary graft failure. Ten patients without platelet engraftment were not alive at 1 month. Two of them had primary graft failure. Complete and mixed donor chimerism were observed in 68 of 92 (73.9%) and 20 of 92 (21.7%) patients respectively, at 1 month after allo-HCT. Eight patients (7.3%) had primary graft failure 1 month after allo-HCT. While 7 patients with primary graft failure died, 1 patient was still alive at the last follow-up. Secondary graft

Table 1 The demographic and clinical features at the time of allogeneic stem cell transplantation

Patients	n: 110 (%)
Gender	
Male	66 (60)
Female	44 (40)
Median age, years*	39.5 (16–67)
Karnofsky performance status	
≥ 90	84 (76.3)
70–90	26 (23.7)
Diagnosis type	
Hodgkin lymphoma	41 (37.3)
Non-Hodgkin lymphoma	69 (62.7)
Stage	
Stage 1–2	10 (9.8)
Stage 3	27 (26.5)
Stage 4	65 (63.7)
Disease status	
Complete response	41 (37.3)
Partial response	37 (33.6)
Stable disease	13 (11.8)
Refractory/progression	19 (17.3)
Response to treatment	
Chemo-sensitive	78 (70.9)
Chemo-refractory	32 (29.1)
Median duration from diagnosis to allo-SCT, months*	26.5 (5–222)
Median number of treatment lines before allo-SCT*	4 (1–8)
Pre-transplantation therapy lines	
≤ 3	49 (45.4)
> 3	56 (54.6)
Prior autologous HCT	
Yes	74 (67.3)
No	36 (32.7)
Donor type	
Match related donor	76 (68.2)
Match unrelated donor	16 (14.5)
Haploidentical	12 (10.9)
Mismatch unrelated	7 (6.4)
Donor–recipient ABO incompatibility	
Yes	48 (43.6)
No	61 (55.5)
Conditioning regimen	
Myeloablative conditioning	29 (26.4)
Reduced intensity conditioning	81 (73.6)
Source of stem cell	
Peripheral blood	109 (99.1)
Bone marrow	1 (0.9)
Median dose of CD34+ stem cells., $\times 10^6$/kg	6.92 (2.1–26.2)
GvHD prophylaxis	
Yes	108 (98.2)
No	2 (1.8)
VOD/SOS prophylaxis	
Yes	61 (55.5)
No	49 (44.5)

Table 1 (continued)

*Median (minimum–maximum)

GvHD graft-versus-host disease, *SCT* stem cell transplantation, *VOD/SOS* veno-occlusive disease/sinusoidal obstruction syndrome

failure occurred in 6 (5.5%) patients during the follow-up period. Two of them were alive at the last flow-up, the others died. Acute GvHD was observed in 34 (30.9%) patients as skin acute GvHD (n:18, 16.3%), gastrointestinal acute GvHD (n:16, 14.5%) and liver acute GvHD (n:8, 7.2%). The median time to acute GvHD was 53.5 (11–240) days. Thirteen patients died. Three of these patients also had chronic GvHD. Chronic GvHD was diagnosed in 17 (15.5%) patients as skin chronic GvHD (n:9, 8.2%), liver chronic GvHD (n:7, 6.3%), lung chronic GvHD (n:5, 4.5%), GIS chronic GvHD (n:3, 2.7%) and eye chronic GvHD (n:1, 0.9%). The median time to chronic GvHD was 255 (119–472) days. Six patients died, 50% due to infection. Sinusoidal obstruction syndrome was detected in 9 (8.2%) patients, 5 (4.5%) of whom were on VOD/SOS prophylaxis. Six had mild VOD/SOS and 3 had severe VOD/SOS. Three patients with severe VOD/SOS died. All received defibrotide as prophylaxis. All had chemo-refractory disease at the time of allo-HCT and 2 of them had a history of previous auto-HCT.

Survival

The mean follow-up time was 67.5 ± 8.1 months (95% CI 51.63–83.42), and the 5-year OS, PFS, and GRFS rates were 38.4% (95% CI 28.2–48.6), 37% (95% CI, 26.6- 47.4), and 34.8% (95% CI 25.6- 44) respectively, for all patients (Fig. 1A–C).

The univariate analyses of prognostic factors to determine 5-year survival including OS, PFS and GRFS are shown in Table 3. Conditioning regimen (22.2% for MAC vs. 44.6% for RIC, $p = 0.018$) (HR: 0.54, 95% CI 0.32–0.92, $p = 0.023$), acute GvHD grade (41.5% for no acute GvHD vs. 56.9% for grades 1–2 vs. 11.5% for grades 3–4, $p = 0.003$) (HR: 0.62, 95% CI 0.26–1.45, $p = 0.266$ vs. HR: 2.21, 95% CI 1.23–3.97, $p = 0.008$), and disease status after allo-HCT (53.5% for CR/PR vs. 3.5% for SD/PD, $p = 0.000$) (HR: 0.16, 95% CI 0.09–0.28, $p = 0.000$) were significantly associated with OS. Conditioning regimen (20.2% for MAC vs. 42.8% for RIC, $p = 0.017$) (HR: 0.52, 95% CI 0.30–0.91, $p = 0.022$), acute GvHD grade (41.1% for no acute GvHD vs. 49% for grades 1–2 vs. 7% for grades 3–4, $p = 0.015$) (HR: 0.71, 95% CI 0.32–1.58, $p = 0.394$ vs. HR: 2.12, 95%, 1.14–3.93, $p = 0.017$), disease status after allo-HCT (48.9% for CR/PR vs. 0% for SD/PD, $p = 0.000$) (HR: 0.11, 95% CI 0.06–0.19, $p = 0.000$), CMV reactivation (22.4% for yes vs. 43% for no, $p = 0.032$) (HR: 0.58, 95% CI 0.34–0.98, $p = 0.04$) and treatment response before allo-HCT (47.5% for chemo-sensitive

Table 2 The outcomes of allogeneic stem cell transplantation

	N: 110 (%)
Post-transplantation disease status	
Complete response	67 (60.9)
Partial response	12 (10.9)
Stable disease	2 (1.8)
Progression	16 (14.5)
Not evaluated	13 (11.8)
Neutrophil engraftment	
Yes	102 (92.7)
No	8 (7.3)
Median time of neutrophil engraftment. days (range)*	13 (8–33)
Platelet engraftment	
Yes	98 (89.1)
No	12 (10.9)
Median time of platelet engraftment, days (range)*	13.5 (8–42)
Acute GvHD	
Yes	34 (30.9)
No	76 (69.1)
Acute GvHD degree	
Grade 1–2	15 (13.6)
Grade 3–4	19 (17.3)
Chronic GvHD	
Yes	17 (15.5)
No	93 (84.5)
Chronic GvHD degree	
Mild	3 (17.6)
Moderate	5 (29.4)
Severe	9 (52.9)
VOD/SOS status	
Yes	9 (8.2)
No	101 (91.8)
CMV reactivation	
Yes	32 (29.1)
No	78 (70.9)
Donor chimerism at 1 month	
≥95%	68 (73.9)
<95%	20 (21.7)
Survival status	
Alive	47 (43.7)
Death	63 (57.3)
Causes of death	
Progression/relaps	17 (26.9)
Infection	23 (36.6)
GvHD	10 (15.8)
VOD	2 (3.2)
Other	11 (17.5)

CMV: Cytomegalovirus; GVHD: Graft-versus-host disease; veno-occlusive disease/sinusoidal obstruction syndrome

vs. 20.9% for chemo-refractory, $p=0.018$) (HR: 1.81, 95% CI 1.08–3.01, $p=0.024$) were significantly associated with PFS. Conditioning regimen (17% for MAC vs. 41% for RIC, $p=0.018$) (HR: 0.56, 95% CI 0.34–0.93, $p=0.025$), acute GvHD grade (40.5% for no acute GvHD vs.51.3% for grades 1–2 vs. 0% for grades 3–4, $p=0.000$) (HR: 0.63, 95% CI 0.28–1.39, $p=0.248$ vs. HR: 3.24, 95% CI 1.84–5.69, $p=0.000$), disease status after allo-HCT (49.5% for CR/PR vs. 0% for SD/PD, $p=0.000$) (HR: 0.14, 95% CI 0.08–0.24, $p=0.000$) and CMV reactivation (20% for yes vs. 41.1% for no, $p=0.030$) (HR: 0.6, 95% CI 0.37–0.98, $p=0.04$) were important prognostic factors for GRFS.

Recipient age/gender/Karnofsky performance status, lymphoma subtype, stage at diagnosis, pretransplant therapy lines, prior auto-HCT, donor-recipient ABO incompatibility, infused CD34+ stem cell dose, acute and chronic GvHD yes/no, VOD/SOS prophylaxis status were not statistically significantly associated with OS, PFS and GRFS.

In multivariate analysis (Table 4), CR/PR disease status after allo-HCT was significantly associated with longer PFS (HR: 13.47, 95% CI 5.80- 31.26, $p=0.000$) and OS (HR: 5.23, 95% CI 2.93- 9.34, $p=0.000$). CR/PR disease status after allo-HCT (HR: 5.79, 95% CI 3.22–10.40, $p=0.000$) and grade 1–2 acute GvHD (HR: 2.33, 95% CI 1.25–4.35, $p=0.008$) were significantly associated with longer GRFS.

Sixty-three (57.3%) patients died and 17 (15.4%) patients died of relapse or progression during follow-up. The 5-year cumulative incidence of NRM was 24.8% (95% CI 12.5-36.7) for all patients (Fig. 2). The most common cause of death was infection-related (n:23, 36.8%) (Table 2). Forty-seven (42.7%) patients are still alive and 41 (37.2%) are alive without disease.

Discussion

Despite new targeted therapies, allo-HCT remains the only curative treatment option for patients with R/R lymphoma. This study analyzed 110 patients with R/R HL or NHL lymphoma who underwent allo-HCT. In this study, the median number of lines of chemotherapy regimens prior to allo-HSCT was 4, and nearly 30% of patients had chemo-refractory disease at the time of transplantation. The median number of lines and the rate of chemo-refractory patients have been reported in the literature to be 3–4 and 23–44.3%, respectively [24–27]. Our results are in line with previous studies. The 5-year OS, PFS, and GRFS rates were 38.4%, 37%, and 34.8%, respectively, with a mean follow-up of 67.5 ± 8.1 months for all patients. The 5-year OS rates were 32.4% and 41.7%, PFS rates were 28.7% and 41.7%, and GRFS rates were 29.3% and 38.2% for HL and NHL, respectively. Ko et al. reported that the 5-year OS and PFS rates with allo-HCT in lymphoma patients were 31.1% and 38.8%,

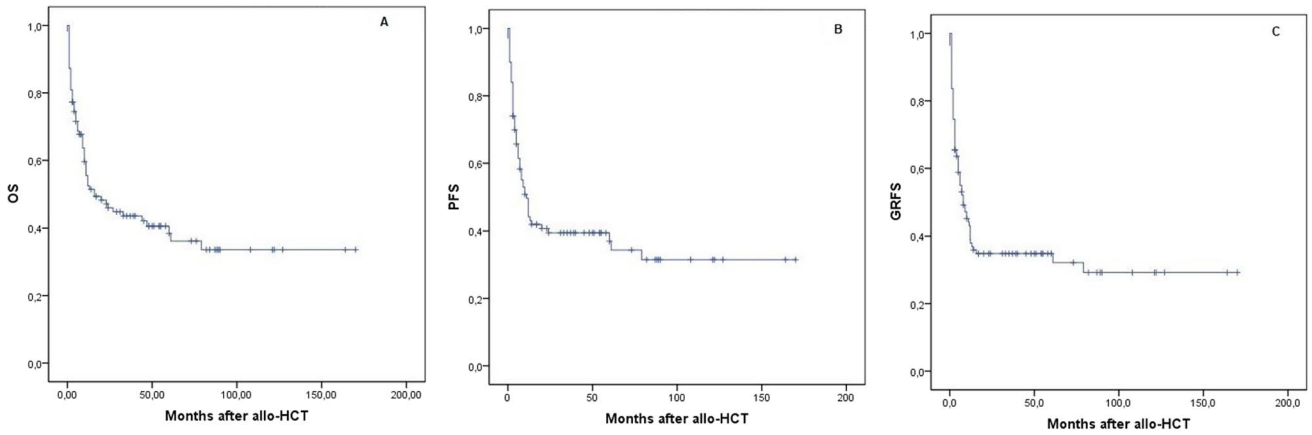

Fig. 1: 1 **A** Overall survival (OS), **B** Progression-free survival (PFS), **C** GvHD-free, relapse-free survival (GRFS)

Table 3 The univariate analyses of prognostic factor to determine 5-year survival including progression-free survival (PFS), overall survival (OS), and graft versus host disease-free, relapse-free survival (GRFS)

Variable	5-year PFS				5-year OS				5 year GRFS			
	%	p	HR (95% CI)	p	%	p	HR (95% CI)	p	%	p	HR (95% CI)	p
Response to treatment												
Chemo-sensitive	47. 5	**0.01**	1.81	**0.02**	45.	0.08			41.	0.12		
Chemo-refractory	20.9	**8**	(1.08–3.01)	**4**	926.9	4			423.5	2		
Conditioning regimen												
Myeloablative	20.2	**0.017**	0.52 (0.30–0.91)	**0.022**	22.2	**0.018**	0.54 (0.32–0.92)	**0.023**	1741	**0.018**	0.56 (0.34–0.93)	**0.025**
Reduced-intensity	42.8				44.6							
Disease status after transplantation												
CR/PR	48.9	**0.000**	0.11 (0.06–0.19)	**0.000**	53.5	**0.000**	0.16 (0.09–0.28)	**0.000**	49.5	**0.000**	0.14 (0.08– 0.24)	**0.000**
SD/PD	0				3.5				0			
Acute GvHD degree												
No acute GvHD	41. 1	**0.015**	Ref	0.39	41. 5	**0.003**	Ref	0.26	40. 5	**0.000**	Ref	0.24
Grade 1–2	49		0.71 (0.32–1.58)	4	56. 9		0.62 (0.26–1.45)	6	51. 3		0.63 (0.28–1.39)	8
Grade 3–4	7		2.12 (1.14–3.93)	**0.017**	11. 5		2.21 (1.23–3.97)	**0.008**	0		3.24 (1.84– 5.69)	**0.000**
CMV reactivation												
Yes	22.4	**0.032**	0.58 (0.34–0.98)	**0.04**	23.3	0.057			20	**0.030**	0.6 (0.37	**0.04**
No	43				44.7				41.1		–0.98)	

$p < 0.05$ are shown in bold

HR hazard ratio, *CI* confidence interval, *CMV* cytomegalovirus, *GvHD* graft-versus-host disease

respectively [24]. In a phase II study evaluating the efficacy of the Fludarabine/Melphalan 100 conditioning regimen in lymphoma patients treated with allo-HCT, the 5-year OS and PFS were 40.4% and 39.2%, respectively [25]. In 2 retrospective studies analyzing the long-term outcomes of patients with R/R HL undergoing allo-HCT, the 5-year OS was 51.4–59%. The 5-year relapse-free survival (RFS), PFS, and GRFS were 38.9%, 49%, and 26%, respectively, in these studies [26, 27]. In another study for R/R aggressive NHL, the 4-year PFS and OS rates were 48% and 47%, respectively [16]. In studies evaluating allotransplantion outcomes in NHL patients, 3-year OS was 45.9–61%, while 3-year DFS and EFS were 45.9% and 50%, respectively [28, 29]. The 5-year PFS, OS, and GRFS results in our long-term study were similar to those in the literature.

In recent years, RIC regimens have become the preferred conditioning regimen in lymphoma due to their low risk of NRM and acceptable survival outcomes. A study from Korea reported that RIC regimen had high survival outcomes with acceptable TRM in patients with lymphoma. In the same study, the 3-year OS, DFS, and TRM with RIC regimen were 62.4%, 59.2%, and 14.9%, respectively [30].

Table 4 The multivariate analyses of the prognostic values for progression-free survival (PFS), overall survival (OS), and graft versus host disease-free, relapse-free survival (GFRFS)

Variables	Hazard ratio	95% CI	*p* value
PFS			
Acute GvHD degree			
No acute GvHD	1	ref	
Grade 1–2	0.39	0.08–1.77	0.226
Grade 3–4	0.90	0.32–2.57	0.848
CMV reactivation			
Yes	1	ref	
No	1.06	0.48–2.35	0.876
Response to treatment			
Chemo-sensitive	1	ref	
Chemo-refractory	1.03	0.49–2.13	0.936
Conditioning regimen			
MAC	1	ref	
RIC	0.53	0.25–1.13	0.100
Disease status after transplantation			
CR/PR	1	ref	
SD/PD	13.47	5.80–31.26	**0.000**
OS			
Conditioning regimen			
MAC	1	ref	
RIC	0.85	0.48–1.50	0.582
Disease status after transplantation			
CR/PR	1	ref	
SD/PD	5.23	2.93–9.34	**0.000**
Acute GvHD degree			
No acute GvHD	1	ref	
Grade 1–2	0.78	0.32–1.87	0.580
Grade 3–4	1.42	0.77–2.62	0.267
GRFS			
Conditioning regimen			
MAC	1	ref	
RIC	0.73	0.43–1.23	0.237
CMV reactivation			
Yes	1	ref	
No	0.93	0.54–1.59	0.794
Disease status after transplantation			
CR/PR	1	ref	
SD/PD	5.79	3.22–10.40	**0.000**
Acute GvHD degree			
No acute GvHD	1	ref	
Grade 1–2	0.77	0.34–1.76	0.539
Grade 3–4	2.33	1.25–4.35	**0.008**

CMV cytomegalovirus, *GvHD* graft-versus-host disease, *MAC* myeloablative conditioning, *RIC* reduced-intensity conditioning, *CI* confidence interval, *CR* complete remission, *PR* partial remission, *SD* stable disease, *PR* progressive disease

In our study, the RIC regimen was mainly used as the conditioning regimen and was significantly superior to the MAC regimen for 5-year OS (RIC: 42.8% vs. MAC: 20.2%), PFS (RIC: 42.8% vs. MAC: 20.2%) and GRFS (RIC: 41% vs. MAC: 17%). Hamadani et al. compared the MAC and RIC/NMA regimens in 533 patients with refractory lymphoma and reported that the RIC regimen had a superior outcome for OS (MAC: 19% vs. RIC/NMA: 28% at three years, $p=0.02$), but two groups had similar outcome for PFS [31]. In contrast, in the other retrospective comparisons of MAC and RIC regimens, the two groups were found to be similar in terms of OS and PFS [32].

In our study, there was a trend for longer 5-year OS, PFS and GRFS in MUD compared to MRD, haploidentical donor and MMUD, but the difference was not significant. In a retrospective study, 3-year PFS was 59%, 44%, and 46% ($p>0.05$), 3-year OS was 52%, 54%, and 67% ($p>0.05$), and 3-year GRFS was 39%, 31%, and 24% ($p>0.05$) for haploidentical donor, MUD and MRD, respectively [33]. Our results were similar to this study. In contrast to our study, Bachanova et al. evaluated the outcomes of alternative donors (MUD, MMUD, or cord blood donors) in patients with lymphoma in which the 3-year adjusted cumulative incidence of relapse was lower after MMUD compared with MUD (25% vs. 33%, $p=0.003$). The 3-year OS was similar at 43% for MUD and 37% for MMUD, so they reported that MMUD could be a suitable donor for patients who lack an HLA-matched sibling or MUD [34].

Although GvHD also affects the outcome of transplantation by inducing transplant-related mortality (TRM), it also has a potential antitumor effect, known as the graft-versus-lymphoma effect, produced by donor T cells [35]. In our study, acute GvHD grade 1–2 positively influenced OS, PFS and GRFS in univariate analysis. However, chronic GvHD had no effect on survival. On multivariate analysis, acute GvHD grade 1–2 was significantly associated with longer GRFS. In a retrospective study, mild stage chronic GvHD showed a superior impact on OS and DFS ($p=0.004$ and $p=0.008$, respectively). However, in the same study, acute GvHD grade ≥ 3 was associated with significantly worse OS and DFS ($p=0.040$ for OS and $p=0.028$ for DFS). In another study, both acute and chronic GvHD were associated with a lower risk of relapse (RR 0.14 and RR 0.15, $p=0.0019$ and $p=0.007$, respectively) [36]. Yoon et al. evaluated 28 R/R NHL undergoing allo-HCT with RIC and reported that patients with chronic GvHD had significantly higher OS and disease-free survival rates than patients without chronic GvHD [30].

CMV reactivation is a critical post-transplant complication that increases transplant-related mortality and morbidity, and CMV disease has been reported in 10–40% of patients after the allo-HCT [37]. In our study, CMV reactivation was observed in 29.1% of patients and was associated

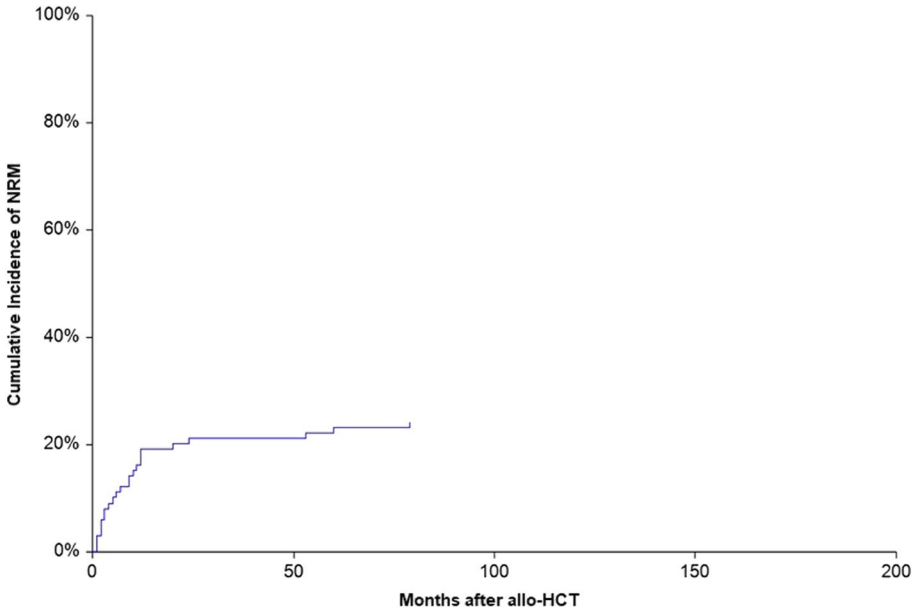

Fig. 2 Cumulative incidence of nonrelapse mortality (NRM)

with significantly worse GRFS and PFS. A retrospective study reported that the 1-year incidence of CMV reactivation in NHL patients was approximately 25%. They found that CMV reactivation was associated with a lower risk of relapse incidence, but the GRFS rate was inferior in the CMV reactivation group, which was found to be an independent predictor of GRFS (HR = 0.325, 95% CI 0.148–0.712, $P = 0.005$) [38]. Our study is consistent with the literature in demonstrating the negative effect of CMV reactivation on GRFS. In another retrospective study, the effect of CMV replication on the risk of relapse was not shown, but decreased OS and increased NRM were associated with CMV replication [39]. However, Koldehoff et al. showed that CMV replication in NHL patients after allo-HCT decreased the risk of relapse [40].

In our study, the 5-year NRM rate was 24.8% (95% CI 12.5–36.7), and the most common cause of death was infection (36.6%) among all lymphoma patients. In a retrospective study from Korea, the 5-year NRM was 28.8% and infection was the main cause of death without disease recurrence or progression [24]. Another retrospective study reported that the cumulative incidence rate of NRM at 3 years was 17.0% in NHL patients [28]. In a phase II study, Lee et al. reported that the 5-year NRM was 21.6% [25]. Another study comparing conditioning regimens (MAC vs. RIC vs. NMA) in NHL patients reported a 5-year NRM of 56% vs. 47% vs. 36%, respectively [41]. In a retrospective study of RR HL patients, the 1-year NRM was 16% [27]. The NRM results in our study were similar to those reported in the literature.

Our study had several limitations. First, it was a retrospective study. Other limitations were that the conditioning regimen protocols, lymphoma subtypes, and donor type were heterogeneously distributed in patients. In addition, the CMV status of donors and patients was not recorded in our study because of the high seropositivity in our country. Despite these limitations, it contributes to the literature in terms of long-term reflection of real-life data in a developing country with high CMV seropositivity.

Conclusion

In conclusion, this retrospective multicenter study evaluated the long-term outcomes of allo-HCT in patients with HL and NHL. According to our results, RIC regimens were the most common conditioning regimen. Transplant outcomes are not influenced by disease subtype. However, the achievement of a CR/PR response after allo-HCT significantly prolongs OS, PFS and GRFS. In addition, the presence of acute grade 1–2 GvHD was found to be another factor prolonging GRFS. Despite the evolution in the treatment of both HL and NHL in recent years, allo-HCT remains the only curative therapy, especially in heavily treated patients. The 5-year OS, PFS, GFRS and NRM results are acceptable despite ~ 30% chemorefractory patients, and support the feasibility of allo-HCT.

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Declarations

Ethical Approval This study was approved by Ege University Ethical Committee (approved number:21-8T/55) and conducted in accordance with the principles of the Helsinki Declaration.

Competing interests The authors declare that they have no competing interests.

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