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Outcomes of Patients with Recurrent and Refractory Lymphoma Undergoing Allogeneic Hematopoietic Cell Transplantation with BEAM Conditioning and Sirolimus- and Tacrolimus-Based GVHD Prophylaxis

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A B S T R A C T

The current standard of care for patients with Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL) is high-dose conditioning followed by autologous stem cell transplantation (ASCT). For some patients (ie, those with highest-risk disease, insufficient stem cell numbers after mobilization, or bone marrow involvement) allogeneic hematopoietic cell transplantation (alloHCT) offers the potential for cure. However, the majority of patients undergoing alloHCT receive reduced-intensity conditioning as a preparative regimen, and studies assessing outcomes of patients after alloHCT with myeloablative conditioning are limited. In this retrospective study, we reviewed outcomes of 22 patients with recurrent and refractory NHL who underwent alloHCT with myeloablative BEAM conditioning and received tacrolimus/sirolimus as graft-versus-host disease (GVHD) prophylaxis at City of Hope between 2005 and 2018. With a median follow-up of 2.6 years (range, 1.0 to 11.2 years), the probabilities of 2-year overall survival and event-free survival were 58.3% (95% confidence interval [CI], 35.0% to 75.8%) and 45.5% (95% CI, 24.4% to 64.3%), respectively. The cumulative incidence of grade II to IV acute GVHD was 45.5% (95% CI, 23.8% to 64.9%), with only 1 patient developing grade IV acute GVHD. However, chronic GVHD was seen in 55% of the patients (n = 12). Of the 22 eligible patients, 2 had undergone previous ASCT and 2 had undergone previous alloHCT. Both patients with previous ASCT developed severe regimen-related toxicity. Patients who underwent alloHCT with chemorefractory disease had lower survival rates, with 1-year OS and EFS of 44.4% and 33.0%, respectively. In conclusion, alloHCT with a BEAM preparative regimen and tacrolimus/sirolimus-based GVHD should be considered as an alternative option for patients with highest-risk lymphoma whose outcomes are expectedly poor after ASCT.

INTRODUCTION

Autologous stem cell transplantation (ASCT) with high-dose conditioning is the current standard of care for patients with relapsed non-Hodgkin lymphoma (NHL) or Hodgkin lymphoma (HL) [1,2]. Outcomes of a large retrospective study reported by the Center for Blood and Marrow Transplant Research comparing the impact of several commonly used high-dose therapy regimens in patients with NHL and HL demonstrated that among patients with HL, a BEAM (BCNU, etoposide, cytarabine, and melphalan) regimen was associated with better survival compared with all other regimens, and indicated variability in toxicity and disease outcomes among specific ASCT regimens [3]. In a more recent retrospective multicenter study, Herrera et al [4] reported that patients with relapsed/refractory NHL, double-hit lymphoma (chromosomal rearrangements in *BCL2* and *MYC*), or double-expressor lymphoma (coexpression of *BCL2* and *MYC* by immunohistochemistry) tend to have inferior outcomes post-ASCT compared with patients with relapsed/refractory NHL lacking these high-risk features [4]. The low survival rates in these high-risk patients demonstrate the need for novel/investigational therapies beyond high-dose chemotherapy and ASCT, including allogeneic hematopoietic cell transplantation (alloHCT).

In patients with NHL or HL with highest-risk disease, patients without sufficient numbers of stem cells due to inefficient mobilization, and patients whose bone marrow is

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involved with lymphoma, alloHCT offers a potential cure. The use of alloHCT with reduced-intensity conditioning (RIC) for patients with relapsed and refractory diffuse large B cell lymphoma with previous unsuccessful ASCT, multiple salvage therapies, advanced age, and/or medical comorbidities has been reported by multiple investigators, with favorable overall survival (OS) of 28% to 49% [5-8]. However, studies assessing outcomes of patients after alloHCT with myeloablative conditioning (MAC) are limited. In 1 retrospective study, alloHCT with MAC was used for NHL, with a 2-year OS of 45% but a high risk of toxicity and treatment-related mortality [9]. Owing to the relatively limited use of MAC in alloHCT, no standard MAC regimen has been established for patients with NHL/HL. Table 1 summarizes recent studies reporting outcomes of alloHCT in patients with recurrent and refractory lymphomas.

The feasibility and tolerance of BEAM as a preparative regimen for alloHCT with tacrolimus and methotrexate (Tac/MTX) as graft-versus-host disease (GVHD) prophylaxis in patients with primary refractory or recurrent low-grade lymphomas was reported for the first time in 1999 by Przepiorka et al [10]. The results of that study were later confirmed by other groups administering BEAM with Campath as GVHD prophylaxis [11,12].

Aberrant cell signaling through the mammalian target of rapamycin (mTOR), phosphatidylinositol-3-kinase/Akt (PI3K/Akt) pathways is shown to be associated with increased metastatic potential and cell proliferation and resistance to chemotherapy in both NHL and HL. mTOR inhibitors (eg, sirolimus) have demonstrated promising results in treatment of lymphoid malignancies [13-15]. We and others have evaluated a combination of tacrolimus/sirolimus (Tac/Siro) as GVHD prophylaxis after alloHCT and found that this combination is associated with reduced incidence/severity of acute GVHD (aGVHD) and nonrelapse mortality (NRM) [16-22]. In patients with lymphoma, administration of sirolimus has been shown to be associated with improved OS after alloHCT in the RIC setting [23]. Results of this retrospective study led to a randomized trial comparing the outcomes between Tac/MTX and Tac/Sir/MTX in RIC HCT. In this trial, addition of sirolimus for GVHD prophylaxis was found to be associated with no increase in overall toxicity and a lower risk of aGVHD, albeit with no improvement in patient survival [24].

Based on this background, we performed a retrospective study aimed at assessing the efficacy of combining alloHCT with a BEAM preparative regimen and Tac/Siro-based GVHD prophylaxis in patients with recurrent and refractory lymphoma.

METHODS

Study Population

Institutional Review Board approval was obtained to review medical records of patients with lymphoma who underwent alloHCT with a BEAM conditioning regimen at City of Hope between 2005 and 2018. A total of 28 patients were identified. Patients who received a transplant from a syngeneic donor (n = 5) or received Tac/MTX as GVHD prophylaxis (n = 1) were excluded from our analysis, leaving 22 patients as the cohort for our final analysis. The majority of patients were selected for alloHCT owing to a high risk of relapse and based on the best clinical judgment of the treating physician. The Disease Risk Index assignment tool [25] was used to retrospectively analyze predicted survival outcomes post-alloHCT.

Table 1
Previous Reports of AlloHCT Outcomes in Patients with Recurrent/Refractory Lymphoma

Report	Number of Patients	Age, yr, median (range)	Resistant Disease, n	Donor Type, %	Conditioning Regimen, %	NRM, % (yr)	Relapse, % (yr)	OS, % (yr)	PFS, % (yr)	aGVHD, %	cGVHD, %
Truelove et al [12]	46	44.8 18-59)	PR, 34; CR1, 22	MSD, 69; MUD, 23; MMUD, 6.6	BEAM-Campath	11 (5)	53 (5)	42 (5)	36 (5)	15	28
Law et al [37]	31	36 (20-60)	CR, 8; PR, 15; IF, 8	MSD, 100	CBV	31 (1)	25 (1)	47 (1)	44 (1)	29	39
Rossi et al [38]	18	42 (18-55)	CR, 10; resistant, 5; therapy-related death, 3	MSD, 100	CBV	17 (3)	27 (3)	76 (2)	56 (2)	22	22
Lazarus [39]	79	46 (21-59)	42	MRD, 100	Cy + TBI (12 Gy)/+ Bu, 82	28 (3)	33 (5)	52 (3)	22 (5)	42	26
Van Kampen et al [40]	101	46 (18-66)	26	MRD, 71; MUD, 29	Cy + TBI (12 Gy)/± VP-16 + Bu, 82	28 (3)	30 (3)	52 (3)	42 (3)	51	42
Bacher et al [41]	396	48 (18-69)	32	MRD, 33; MUD, 67	MAC: Cy + TBI (12 Gy)/ + Bu, 77	56 (5)	26 (5)	18 (5)	18 (5)	43	37
Rezvani et al [42]	32	52 (18-67)	72	MRD, 66; MUD, 34	Flu/TBI (2 Gy)	25 (3)	41 (3)	45 (3)	35 (3)	53	44
Hamdani et al [8]	MAC, 307	46 (19-66)	100	MSD, 60; MUD, 30; MMUD, 10	Cy/TBI; Bu/Cy	53 (3)	28 (3)	19 (3)	19 (3)	29	33
	RIC, 226	53 (20-70)	100	MSD, 47; MUD, 31; MMUD, 23	Flu/Mel; Flu/Bu ± TBI	42 (3)	35 (3)	28 (3)	23 (3)	31	38
Glass et al [43]	84	48 (18-65)	Rituxan, 55	MSD, 31; MUD, 33; MMUD, 36	Flu/Bu/Cy+ rituxan	34 (1)	29 (1)	52 (4)	45 (1)	46	33
			No rituxan, 55	MSD, 24; MUD, 48; MMUD, 26	Flu/Bu/Cy	37 (1)				42	41
Thomson et al [7]	48	46 (23-64)	17	MRD, 62; MUD, 38	Flu/Mel + Campath	32 (4)	33 (4)	47 (4)	48 (4)	17	22
Brammer et al [31]	22	46 (20-62)	9	Haplo	Flu/Mel/TBI (2 Gy)	20 (1)	27 (2)	54 (2)	54 (2)	51	3
Dietrich et al [44]	59	N/A	N/A	Haplo	Flu/Bu ± TBI or Flu/TBI	25 (2)	27 (2)	56 (2)	50 (2)		
Kanate et al [32]	185	55 (18-75)	5.4	Haplo	Flu/Cy/TBI (2 Gy)	16 (2)	34 (2)	63 (2)	50 (2)	8	13

PR, partial remission; MSD, matched sibling donor; MRD, matched related donor; MMUD, mismatched unrelated donor; IF, induction failure; CBV, cyclophosphamide, BCNU (carmustine), and VP16; haplo, haploidentical; Cy, cyclophosphamide; TBI, total body irradiation; Flu, fludarabine; Mel, melphalan; Bu, busulfan; N/A, not available.

Transplantation Procedure

All patients received high-dose conditioning with a BEAM regimen as follows: BCNU 300 mg/m^2 on day -6, etoposide 200 mg/m^2 on days -5 to -2 (total dose, 800 mg/m^2), cytarabine 400 mg/m^2 on days -5 to -2 (total dose, 1600 mg/m^2), and melphalan 140 mg/m^2 on day -1. Allogeneic stem cells were infused on day 0. GVHD prophylaxis comprised i.v. tacrolimus infusion starting at .02 mg/kg started on day -3 and sirolimus at a 12-mg loading dose on day -3, followed by 4 mg/day orally. Sirolimus and tacrolimus levels were subsequently adjusted based on trough levels checked twice weekly. Patients were monitored for laboratory values indicating thrombotic microangiopathy. All patients received standard antimicrobial prophylaxis with Bactrim loading until day -3, micafungin 50 mg i.v. daily starting on day +1, and acyclovir for zoster prophylaxis on day -1.

Outcome Definitions and Statistical Analyses

Descriptive statistics were used to summarize baseline patient demographic, treatment, and disease characteristics. Survival estimates were calculated using the Kaplan-Meier method. OS was defined as the time from transplantation to death from any cause, and event-free survival (EFS) was defined as the time from transplantation to relapse/progression or death from any cause. The cumulative incidences of relapse/progression, NRM, aGVHD, and chronic GVHD (cGVHD) were estimated using competing risks. Relapse/progression was defined as the time from transplantation to relapse or progression, with NRM as a competing risk. NRM was defined as the time from transplantation to death from any cause other than relapse/progression, with relapse or progression as a competing risk. aGVHD was defined as the time to onset of grade II-IV aGVHD, with relapse and death as competing events. cGVHD was defined as the time to onset of any cGVHD, with relapse and death as competing events.

RESULTS

Patient Characteristics

The median age of patients and donors at the time of transplantation was 46 years (range, 18 to 61 years) and 52 years (range, 29 to 63 years), respectively. Of the 22 eligible patients, 16 (72.7%) had NHL, 5 had HL (22.7%), and 1 (4%) had histiocytic sarcoma evolved from previous follicular lymphoma. In the NHL subgroup, 10 patients (62.5%) had diffuse large B cell lymphoma. The majority of patients were selected for alloHCT due to high risk of relapse, and 45% of patients (n = 10) had primary refractory disease requiring multiple lines of salvage chemotherapy to enter remission. Disease status at the time of HCT was complete remission (CR) 1 in 1 patient (4%), CR2 or greater in 9 patients (40.9%), refractory disease in 9 patients (40.9%), and partial response (chemosensitive) in 3 patients (13.6%) (Table 2). Patients were heavily pretreated, with a mean of 3.6 (range, 2 to 7) lines of previous therapy. The Disease Risk Index was high risk in 8 patients and very high risk in 13 patients, predicting a 2-year OS of 34% (95% confidence interval [CI], 32% to 36%) and 24% (95% CI, 17% to 31%) respectively. One patient had an intermediate risk score. Donors were matched sibling donors matched unrelated donors (MUDs) in 11 patients (50.0%). Four of the 11 MUD transplant recipients (18.2%) received a transplant from a 9/10 HLA-matched donor, and GVHD prophylaxis consisted of Tac/Siro and mini MTX. The remaining 7 MUD transplant recipients received a transplant from a 10/10 HLA-matched donors and Tac/Siro only as GVHD prophylaxis.

Table 2
Patient and Disease Characteristics

Characteristic	Value
Age, yr, median (range)	
Patient	46 (18-61)
Donor	52 (29-63)
Sex, n (%)	
Male	16 (72.7)
Female	6 (27.3)
Donor, n (%)	
Male	14 (63.6)
Female	8 (36.4)
Diagnosis, n (%)	
HL	5 (22.7)
NHL	16 (72.7)
Diffuse large B cell lymphoma	10 (45.5)
PTCL	1 (4.5)
BL	1 (4.5)
Follicular lymphoma	1 (4.5)
Transformed follicular lymphoma	1 (4.5)
Natural killer/T cell	1 (4.5)
ALCL	1 (4.5)
Histiocytic sarcoma	1 (4.5)
Disease status, n (%)	
CR2 or greater	9 (40.9)
CR1	1 (4.5)
Refractory	9 (40.9)
Partial response	3 (13.6)
Donor type, n (%)	
Sibling	11 (50.0)
Unrelated	11 (50.0)
Graft source, n (%)	
Bone marrow	1 (4.5)
Peripheral blood stem cells	21 (95.5)
HLA match, n (%)	
Matched	18 (81.8)
Mismatched	4 (18.2)
GVHD prophylaxis, n (%)	
Tacrolimus/sirolimus	18 (81.8)
Tacrolimus/sirolimus/methotrexate	4 (18.2)
Previous HCT, n (%)	
Allogeneic	2 (9.1)
Autologous	2 (9.1)
Lines of previous therapy, median (range)	3.6 (2-7)
Disease Risk Index, n (%)	
Intermediate	1 (4.5)
High risk	8 (36.4)
Very high risk	13 (59.1)

PTCL, peripheral T cell lymphoma; BL, Burkitt lymphoma; ALCL, anaplastic large cell lymphoma.

Transplantation Outcomes

All patients engrafted successfully, with a median time to neutrophil engraftment of 13 days (range, 10 to 24 days). The median duration of follow-up for living patients was 2.6 years (range, 1.0 to 11.2 years), with 2-year probabilities of OS and EFS of 58.3% (95% CI, 35.0% to 75.8%) and 45.5% (95% CI, 24.4% to 64.3%), respectively (Table 4, Figure 1A and B). The cumulative incidences of relapse and NRM at 2 years were 31.8% (95% CI, 13.6% to 51.8%) and 22.7% (95% CI, 8.0% to 42.0%), respectively (Table 4). aGVHD was noted in 11 patients (50%), 10 of whom developed grade II to IV aGVHD, with a cumulative incidence of 45.5% (95% CI, 23.8% to 64.9%). Only 1 patient developed grade IV aGVHD. The cumulative incidence of cGVHD was 45.5% at 1 year (95% CI, 23.4% to 65.2%), with extensive/severe GVHD in the majority of patients (n = 10) (Table 3).

Sinusoidal obstruction syndrome (SOS) was noted in 4 patients (18%). All 4 patients were successfully treated with defibrotide, with complete resolution of clinical symptoms and radiologic features. Two of the 4 patients who developed SOS had undergone previous alloHCT. One of the 4 patients who developed SOS had undergone multiple courses of

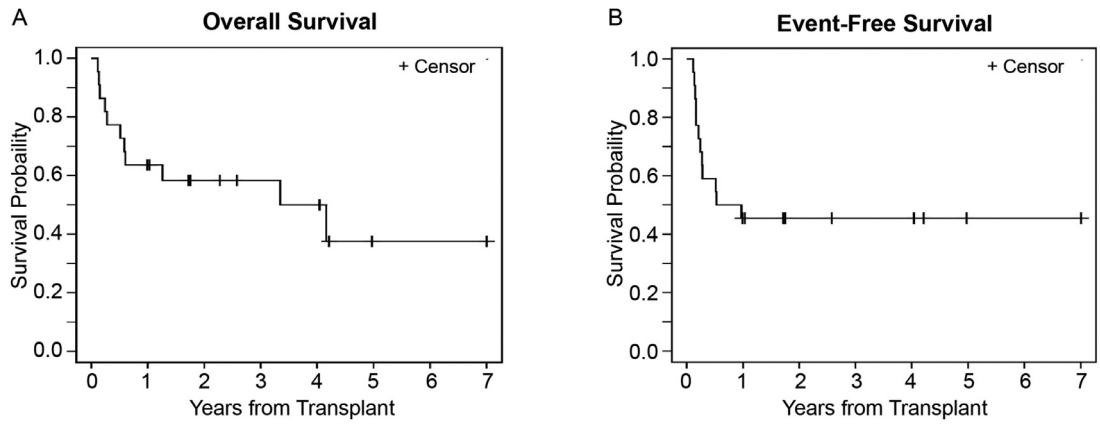

Figure 1. Survival probability curves. (A) OS. (B) EFS.

chemotherapy (CR-3), and the fourth patient had intestinal T cell lymphoma with hepatic involvement at diagnosis. Post-transplantation thrombotic microangiopathy (TMA) was diagnosed in 2 patients (9%) in our cohort.

Causes of death (n = 11) were disease progression in 4 patients; infection, diffuse alveolar hemorrhage, aGVHD, cGVHD, sepsis, and multiorgan failure in 1 patient each, and unknown in 2 patients (Table 3). Although the incidence of acute and cGVHD was high in our cohort, GVHD-related mortality rates were low, with only 2 patients dying from complications due to either aGVHD or cGVHD. The incidences of aGVHD and cGVHD in this report are consistent with the prevailing rates at our institution.

Impact of Previous Transplantation

Four patients in this study had undergone previous transplantation, including 2 with alloHCT and 2 with ASCT. Both patients who underwent ASCT using BEAM conditioning developed severe regimen-related toxicity and died from pulmonary complications, presumably related to cumulative pulmonary toxicity from repeat BCNU exposure. One patient with previous alloHCT developed gastrointestinal GVHD and fungal pneumonia and died. Among 18 patients, excluding 4 with previous alloHCT, the 2-year OS and EFS were 65.7% (95% CI, 38.7% to 83.0%) and 50.0% (95% CI, 25.9% to 70.1%), respectively.

Adverse outcomes were noted in chemorefractory patients (n = 9) compared with chemosensitive patients (n = 13) before alloHCT. The 2-year OS and EFS estimates were 33.3% (95% CI, 7.8% to 62.3%) and 33.3% (95% C,: 7.8% to 62.3%), respectively, in chemorefractory patients, compared with 76.9% (95% CI, 44.2% to 91.9%) and 53.8% (95% CI, 24.8% to 76.0%) in patients with chemosensitive lymphoma pre-alloHCT. No difference in any of the clinical endpoints was noted between the patients with NHL and those with HL.

Table 3
Transplantation Outcomes

Outcomes (n = 22)	Value
aGVHD	
Yes, n (%)	11 (50.0)
Grade I	1
Grade II	8
Grade III	1
Grade IV	1
No, n (%)	11 (50.0)
cGVHD	
Yes, n (%)	12 (54.5)
Limited	2
Extensive	10
No, n (%)	5 (22.7)
Not evaluable (died <100 days), n (%)	5 (22.7)
Relapse, n (%)	
Yes	7 (31.8)
No	15 (68.2)
Vital status, n (%)	
Alive	11 (50)
Dead	11 (50)
Cause of death, n (%)	
Disease progression	4 (36.4)
Infection	1 (9.1)
DAH	1 (9.1)
aGVHD	1 (9.1)
cGVHD	1 (9.1)
ARDS/MODS	1 (9.1)
UK	2 (18.2)

DAH, diffuse alveolar hemorrhage; ARDS/MODs, adult respiratory distress syndrome/multi-organ failures; UK, unknown.

Table 4
Point Estimates for Outcomes

Outcome	100 Days	1 Year	2 Years
OS, %	81.8 (58.8-92.8)	63.6 (40.3-79.9)	58.3 (35-78.5)
EFS, %	63.6 (40.3-79.9)	45.5 (24.4-64.3)	45.5 (24.4-64.3)
NRM, %	18.2 (5.5-36.8)	22.7 (8.0-42.0)	22.7 (8.0-42.0)
CIR, %	18.2 (5.4-36.9)	31.8 (13.6-51.8)	31.8 (13.6-51.8)
aGVHD, %	45.5 (23.8-64.9)		
cGVHD, %		45.5 (23.4-65.2)	

Data are median (range).
CIR, cumulative incidence of relapse.

DISCUSSION

Advances in immunochemotherapy over the past decade have helped improved clinical outcomes of patients diagnosed with NHL and HL. The most recent Surveillance, Epidemiology, and End Results (SEER) database from 2008 to 2014 shows a 5-year survival of 71.4% for patients diagnosed with NHL and 86.6% for those diagnosed with HL. Unfortunately, however, relapse and refractory disease remain significant challenges in the treatment of these patients with a uniformly poor prognosis [26-28]. In a recent retrospective study, patients with aggressive chemoresistant B cell lymphomas relapsed within 1 year post-ASCT, with a reported median OS of 6 months [29]. In the Collaborative Trial in Relapsed Aggressive Lymphoma (CORAL) study, subgroup of patients failing rituximab-based treatment within 12 months of diagnosis had poor outcomes with ACST, with a 3-year PFS of only 23% [30], showing a major limitation in treating high-risk patients with ASCT and demonstrating the need to develop more

effective therapies, including alloHCT. However, the most effective conditioning regimen for alloHCT in the setting of aggressive lymphomas remains unknown.

The feasibility and tolerance of BEAM as a preparative regimen for alloHCT and Tac/MTX-based GVHD prophylaxis was first reported by Przepiorka et al [10], in 30 patients with refractory or recurrent low- and intermediate-grade lymphoma. Twenty-three patients achieved a complete remission post-alloHCT, with a 2-year relapse rate of 23%, OFS of 48%, and disease-free survival of 42%. In aggressive lymphoma setting, Truelove et al [12], reported outcomes of 46 patients with relapsed refractory aggressive NHL who underwent alloHCT with a BEAM-Campath preparative regimen, with OS of 54% and 42% and PFS of 41% and 36% at 1 and 5 years, respectively.

Recently, promising results have been reported in haploidentical transplantation setting using RIC, with 2-year PFS and relapse rates of 54% and 27%, respectively [31]. Similar results were reported by Kanate et al [32] in an RIC setting, with 3-year PFS and relapse rates of 47% and 36%, respectively, and very low rates of aGVHD and cGVHD (8% and 13%, respectively). However, in both studies, the number of patients with chemorefractory disease in the haploidentical RIC arm was low (9% and 5%, respectively), and prospective studies for patients with chemoresistant disease are needed to evaluate for a PFS benefit in these high-risk patients. Table 1 summarizes of previous reports of transplantation outcomes in patients with refractory and recurrent leukemia.

Using BEAM conditioning with Tac/Siro as GVHD prophylaxis, our outcomes (2-year OS of 65.7% and EFS of 50% in 18 patients without previous transplantation) compare favorably to previous reports [12]. Of note, although our study cohort was small, our patient population had a higher risk of disease relapse based on disease status at the time of alloHCT compared with other reports. Our improved EFS could be due to a combination of BEAM conditioning and the antilymphoma activity conferred by sirolimus used in GVHD prophylaxis. In our cohort, rates of aGVHD and cGVHD were high (50%) for these high-risk patients, indicating the need for better GVHD prophylaxis regimens to improve GVHD/relapse-free survival outcome. Given the high risk of post-alloHCT relapse, it is possible that treating physicians might have been more aggressive in terms of tapering immune suppression. Such strategies as post-transplantation high-dose cyclophosphamide have the potential to reduce the rate of GVHD-related morbidity, although this type of post-transplantation treatment should be balanced with the risk of relapse.

In this high-risk population with aggressive lymphoma receiving BEAM conditioning and Tac/Siro-based prophylaxis, 2 subgroups had worse outcomes. The first group was patients who underwent alloHCT with chemorefractory disease, associated with 1-year OS and EFS of 44.4% and 33.0%, respectively, indicating the need to optimize disease control before alloHCT. Effective graft-versus-lymphoma activity develops over a period of 3 to 6 months post-alloHCT, and our results indicate that increasing the conditioning intensity using BEAM is insufficient to overcome the high relapse rate associated with chemorefractory lymphoma. The second subgroup was patients with previous allogeneic or autologous HCT, associated with an unacceptably high risk of NRM due to pulmonary toxicity, SOS, and severe GVHD/infection in our 4 patients. Based on our data, caution is indicated when recommending the use of BEAM-alloHCT in patients with previous HCT and chemorefractory lymphomas.

Finally, with the advent of immunotherapy, outcomes for high-risk patients with recurrent refractory lymphoma have been revolutionized. Neelapu et al [33] reported results of a phase 2 study in 111 patients with refractory B cell lymphomas who were treated with anti-CD19 CAR T cells (axicabtagene ciloleucel), showing an overall response rate of 82% and a complete response rate of 54%. The 18-month OS was 52%, with rates of primary grade 3 toxicity of cytokine-release syndrome and neurologic toxicity of 13% and 28%, respectively. Similarly exciting outcomes have been reported with checkpoint inhibitors in relapsed refractory HL, with an overall response rate of 78%, with 17% complete responses [34]. However, long-term follow-up on the efficacy of CAR T cell therapy is not yet available, and to date no survival plateau has been achieved for checkpoint inhibition in relapsed and refractory HL [35,36]. Therefore, alloHCT may have a continued role in disease control in the subset of patients with NHL and HL [34] who experience incomplete remission after chemotherapy, cellular therapy, or checkpoint inhibitor therapy.

In conclusion, our results demonstrate that alloHCT with a BEAM preparative regimen and Tac/Siro-based GVHD offers an alternative option for patients with highest-risk lymphoma whose outcomes are expectedly poor after ASCT.

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Conflict of interest statement: Conflict of interest relevant to this work.

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