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Haploidentical

Multicenter Phase II Study on Haploidentical Bone Marrow Transplantation Using a Reduced-Intensity Conditioning Regimen and Posttransplantation Cyclophosphamide in Patients with Poor-Prognosis Lymphomas

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Allogeneic stem cell transplantation from haploidentical donors using unmanipulated bone marrow and posttransplantation cyclophosphamide has been largely employed to cure high-risk lymphomas. However, the increased incidence of relapse associated with the use of a nonmyeloablative conditioning regimen is still considered a concerning issue. The aim of our study was to prospectively evaluate the efficacy and feasibility of a reduced-intensity conditioning regimen, including thiotepa, cyclophosphamide, and fludarabine, in high-risk lymphoma patients. This was a prospective multicenter study. We enrolled 49 patients, of whom 47 were evaluable. Graft source (bone marrow) and graft-versus-host disease (GVHD) prophylaxis were the same for all patients. The primary endpoint was the proportion of patients free of disease progression at 1 year. The primary endpoint was met, as 29 out of 47 patients were alive and free of disease at 1 year (1-year progression-free survival, 60%). Forty-five recipients engrafted and achieved full donor chimerism at day 100. The cumulative incidences (CIs) of ANC engraftment at 30 days and platelet engraftment at 60 days were 89% and 83%, respectively. Two patients experienced graft failure. The CIs of day 100 grades 2 to 4 acute GVHD and 2-year moderate-to-severe chronic GVHD were 26% and 16%, respectively. With a median follow-up of 47.5 months (range, 22 to 74), the 4-year progression-free survival and overall survival were 54% and 64%, respectively. The 4-year CI of relapse was 28%, and the 4-year nonrelapse mortality was 15%. Thiotepa-based reduced-intensity conditioning was well tolerated with encouraging survival in a cohort of patients with poor-prognosis lymphoma. Both the incidence of relapse and nonrelapse mortality were acceptable.

INTRODUCTION

Lymphoma patients refractory to several lines of chemotherapy or relapsing after high-dose chemotherapy with autologous stem cell support have a poor prognosis with short survival [1,2]. Possible therapeutic options for these patients include monoclonal antibodies, which are currently in early-

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phase studies, chimeric antigen receptor T cells for specific histological subtypes, and allogeneic stem cell transplantation (allo-SCT). Adoptive immunotherapy through allo-SCT is effective even if severe toxicities, mainly graft-versus-host disease (GVHD) and infections, do still contribute significantly to increased morbidity and mortality. Furthermore, matched related donors (MRDs) and matched unrelated donors (MUDs) are not available for all patients; thus, alternative donors (mismatched unrelated donors, haploidentical donors, and cord blood) are being increasingly selected for donation. In the last 10 years, a growing number of allo-SCTs have been performed using haploidentical donors without T cell depletion. Although several T cell-replete platforms are available with different GVHD prophylactic regimens, the most frequently used in the United States and in Europe is posttransplantation cyclophosphamide (PT-Cy), as pioneered by The Johns Hopkins Comprehensive Transplant Center [3,4]. A pivotal study based on a truly nonmyeloablative conditioning (NMAC) regimen confirmed the feasibility and tolerability of this platform; however, the relapse rate was 58% at 2 years, although it was significantly lower in lymphoma patients [4]. Several factors could underpin this high relapse rate, such as active disease at transplantation, a heavily pretreated patient population, and the lack of anti-lymphoma activity of the conditioning regimen. Based on this background, we planned a prospective multicenter phase II study to test a reduced-intensity conditioning (RIC) regimen, already extensively used in the Gruppo Italiano per il Trapianto di Midollo Osseo, Cellule Staminali Emopoietiche e Terapia Cellulare (GITMO) centers [5], containing active drugs against lymphoma such as thiotepa, cyclophosphamide, and fludarabine. The original conditioning regimen was modified by adding low-dose total body irradiation (TBI; 2 Gy) or total marrow irradiation (TMI)/total lymphoid irradiation (TLI), as applicable, to limit the risk of graft failure.

METHODS

From 2011 to 2018, 49 patients with lymphoma with a poor prognosis were enrolled in the trial; 47 of these patients were evaluable. This trial was registered at ClinicalTrials.gov with the identifier NCT02049580.

Inclusion Criteria

Patients fulfilling the following general criteria were considered eligible: (1) Patients had to provide a signed and dated Institutional Ethics Committee (IEC)-approved informed consent. (2) Patients had to be ≥18 years of age, with an upper age limit of 70 years. (3) Patients had to have a Karnofsky performance status score ≥ 80%. (4) Human leukocyte antigen (HLA) typing was performed at high resolution (allele level) for HLA-A, HLA-B, HLA-Cw, HLA-DRB1, and HLA-DQB1 loci, and a minimum match of 5/10 was required. (5) Patients who had no HLA-identical siblings or 10/10 unrelated donors were eligible; however, an unrelated donor search was not required for a patient to be eligible for this protocol if the clinical situation dictated urgent transplantation. Donors and recipients were required to have at least one identical allele, as determined by high-resolution typing, of each of the following genetic loci: HLA-A, HLA-B, HLA-Cw, HLA-DRB1, and HLA-DQB1. (6) Also eligible were patients with lymphoma (any histological subtype) who relapsed after high-dose chemotherapy and were in partial remission or complete remission or with stable disease after the last chemotherapy (CT) line.

The disease-related inclusion criteria were as follows: (1) Hodgkin lymphoma—patients who were refractory to at least two CT lines; a strategy of tandem autologous transplantation and allo-SCT was allowed. (2) Diffuse large B cell lymphoma—patients who were refractory to second-line salvage chemotherapy (patients in partial remission or with stable or progressive disease). These patients had to be in partial remission or complete remission or have stable disease after one or more further CT lines; transformed low-grade lymphomas were included. (3) Peripheral T cell lymphoma—patients who failed to achieve complete remission after first-line CT. (4) Low-grade lymphomas (follicular and not follicular)—patients refractory to rituximab-containing regimens or relapsing after at least two lines of CT; the duration of first remission was <1 year. (5) Chronic lymphocytic leukemia—patients with refractory or relapsing (response duration < 1 year) disease after rituximab–fludarabine CT. (6) Mantle cell lymphoma—patients relapsing or refractory to first-line conventional CT.

Patient-related inclusion criteria were as follows: adequate organ function as measured by left ventricular ejection fraction at rest ≥ 40%; bilirubin ≤ 2.5 mg/dL; alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase ≤ 5× the upper limit of normal; creatinine clearance or glomerular filtration rate ≥ 50 mL/min/1.73/m^2; forced expiratory volume in 1 second, forced vital capacity, and diffusing capacity of carbon monoxide ≥ 50% predicted (corrected for hemoglobin); and, if unable to perform pulmonary function tests, then O_2 saturation ≥ 92% in room air.

Donor Selection Criteria

Donor selection criteria included the following: (1) Donors had to provide signed and dated IEC-approved informed consents. (2) Donors had to be HLA-haploidentical first-degree relatives of the patient; eligible donors included biological parents, siblings, children, or half-siblings. (3) Donors had to be ≥18 years of age. (4) Donors had to meet the selection criteria as defined by the Joint Accreditation Committee of ISCT and EBMT. (5) Donors had to display an absence of donor-specific antibodies against HLA antigens.

Conditioning Regimen and Stem Cell Source

All patients received the same conditioning regimen, which is reported in Table 1. The RIC regimen consisted of thiotepa 10 mg/kg on day −6; fludarabine 30 mg/m^2 from day −5 to day −2; cyclophosphamide 30 mg/kg on day −5; and low-dose (2 Gy) TBI or TMI/TLI on day −1 (since March 2016). All patients received bone marrow as a stem cell source on day 0.

GVHD Prophylaxis and Diagnosis

GVHD prophylaxis consisted of PT-Cy 50 mg/kg on days +3 and +4 and cyclosporine A or tacrolimus and mycophenolate mofetil (MMF) starting from day +5. The calcineurin inhibitors were reduced starting from days +90 to 100, and MMF was stopped after day +35. Acute GVHD (aGVHD) was graded according to Consensus criteria [6], and chronic GVHD (cGVHD) was retrospectively graded following the National Institutes of Health criteria [7]. Hyperacute GVHD was defined as that occurring within 14 days after transplantation [8].

Engraftment

Neutrophil engraftment was defined as the first of 3 consecutive days with an absolute neutrophil count (ANC) of 0.5 × 10^9/L after transplantation. Platelet engraftment was defined as a platelet count of 20 × 10^9/L, with no transfusions during the preceding 7 days. Granulocyte colony-stimulating factor (G-CSF) was started on day +5.

Statistical Analysis

This study was a Fleming single-arm, single-stage, phase II, multicenter study of an RIC regimen before haploidentical bone marrow infusion and posttransplantation cyclophosphamide. The primary endpoint of this study was the 1-year progression-free survival (PFS) rate. It was assumed that a 1-

Table 1
RIC Regimens Used in the Trial

Day −6	Day −5	Day −4	Day −3	Day −2
TT (10 mg/kg)	F (30 mg/m^2) Cy (30 mg/kg)	F (30 mg/m^2)	F (30 mg/m^2)	F (30 mg/m^2)
Day −1	Day 0	Day +3	Day +4	Day +5
TBI or TMLI (200 cGy)	BM infusion	Cy (50 mg/kg)	Cy (50 mg/kg)	FK (1 mg/kg) or CSA (3 mg/kg) MMF (45 mg/kg) G-CSF (5 μg/kg)

TT indicates thiotepa; F, fludarabine; Cy, cyclophosphamide; BM, bone marrow; FK, tacrolimus; CSA, cyclosporin A; MMF, mycofenolate mofetil; G-CSF, granulocyte colony-stimulating factor.

year proportion of progression-free patients of 20% or lower would be considered to be clinically unworthy of analysis, whereas a proportion of 40% or higher would be assumed to be of potential interest. The associated alpha and beta errors were set to .05 (one-sided) and .10, respectively. This design required the recruitment of at least 47 patients; at least 15 progression-free patients at 1 year had to be observed to consider the treatment of interest.

Table 2
Patient Characteristics (N = 47)

Characteristics	Value
Follow-up (mo), median (range)	37 (16–63)
Patient age (yr), median (range)	43 (20–68)
Donor age (yr), median (range)	42 (21–71)
Gender (M/F), n	25/22
Disease type	
HL, n (%)	23 (49)
B cell NHL, n (%)	16 (34)
DLBCL, n	7
Follicular, n	2
GZ, n	2
CLL, n	1
Richter CLL, n	1
MCL, n	1
Unknown, n	2
T cell NHL, n (%)	8 (17)
NOS, n	5
AITL, n	1
MF, n	1
SS, n	1
Previous HDC, n (%)	
Yes	29 (62)
No	18 (38)
Disease status pre-allo, n (%)	
CR	24 (51)
PR	19 (40)
SD	4 (9)
HCT-CI, n (%)	
0–1	17 (35)
2	12 (25)
≥3	28 (40)
CMV serostatus, n (%)	
Positive/positive	30 (64)
Negative/positive	6 (13)
Positive/negative	6 (13)
Negative/negative	5 (11)
Sex mismatch, n (%)	
Others	38 (81)
Female → male	9 (19)
ABO compatibility, n (%)	
Compatible	29 (62)
Minor	10 (21)
Major	7 (15)
Major/minor	1 (2)
Donor relationship, n (%)	
Sibling	24 (51)
Parent	13 (28)
Child	10 (21)

HL indicates Hodgkin lymphoma; NHL, non-Hodgkin lymphoma; DLBCL, diffuse large B-cell lymphoma; GZ, gray zone; CLL, chronic lymphocytic leukemia; MCL, mantle cell lymphoma; NOS, not otherwise specified; AITL, angioimmunoblastic T cell lymphoma; MF, mycosis fungoid; SS, Sezary syndrome; CR, complete remission; PR, partial remission; SD, stable disease; HCT-CI, Hematopoietic Cell Transplantation-Comorbidity Index; CMV, cytomegalovirus.

A nonrelapse mortality (NRM) of 10% or lower would be clinically desirable; conversely, an NRM ≥ 30% was assumed to be clinically unacceptable. The RIC regimen was then considered potentially dangerous, with a 15% rejection error and a power of 80%, if ≥3 of the first 15 enrolled patients (20%) experienced death due to toxicity during the first 30 days after transplantation. In such circumstances, study enrollment would be halted.

The toxicity and safety data are summarized as frequencies and proportions, whereas continuous data are summarized as medians (ranges). Survival analysis was performed by plotting survival curves according to the Kaplan–Meier method. Hazard ratios were calculated using the Cox proportional hazard model. Cumulative incidence curves were also generated. PFS was defined as the time from starting the RIC regimen to the first documented disease recurrence by radiological assessment or death due to any cause, whichever occurred first. The PFS rate was defined as the proportion of patients alive and free of disease at 1 and 4 years. Overall survival (OS) was defined as the time from starting the RIC regimen to death due to any cause or last contact for patients who were alive. GVHD-free, relapse-free survival (GRFS) was defined as the time from initiation of the RIC regimen to the appearance of grades 3 or 4 acute GVHD, chronic GVHD requiring systemic treatment, relapse, death, or last contact, whichever occurred first. Time to ANC and platelet engraftment was defined starting from RIC regimen initiation to engraftment or death. The cumulative incidence of relapse and NRM were calculated from the start of the RIC regimen until relapse, death, or last contact for alive and disease-free patients. aGvHD was calculated from the start of RIC until aGvHD, death, or 180 days for alive and aGvHD-free patients, whereas cGvHD was calculated only for patients surviving at least 100 days until cGvHD or death or last contact for patients who were alive without cGvHD. $P \leq .05$ was considered to be statistically significant. All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC), R 3.4.1 (R Foundation for Statistical Computing, Vienna, Austria), and Stata 14 (StataCorp, College Station, TX).

RESULTS

Patient characteristics are reported in Table 2. Forty-nine patients were included, and 47 were evaluable. Two patients did not receive transplantation because of early progression. Half of the patients were transplanted for Hodgkin lymphoma, 62% of patients relapsed after high-dose chemotherapy, and all but four were in complete remission (CR) or partial remission (PR) before allo-SCT. The median follow-up of patients who were alive was 47.5 months (range, 22 to 74).

Engraftment

The median times to obtain a safe ANC and untransfused platelet count were 22 days (range, 14 to 44) and 27 days (range, 17 to 151), respectively. The cumulative incidences of ANC engraftment at day +30 and platelet engraftment at day +60 was 89% (95% confidence interval [CI], 75 to 95) and 83%

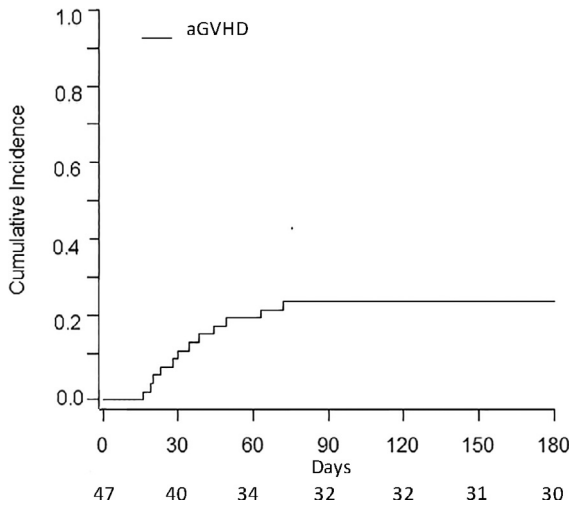

Figure 1. Cumulative incidence of grades 2 to 4 aGVHD.

Table 3
Clinical Results for the Whole Population

	PFS (%)	OS (%)	Relapse Rate (%)	NRM (%)	GRFS (%)
At 1 yr	60	75	26	15	58
At 2 yr	58	68	28	15	55
At 3 yr	58	68	28	15	55
At 4 yr	54	65	28	19	52

(95% CI, 71 to 94), respectively. Two patients had graft failure: one secondary to infection and one primary. One patient received a boost with CD34-positive selected stem cells because of poor graft function. All other evaluable patients obtained full donor chimerism at day +100.

GVHD

The 6-month cumulative incidence of grades 2 to 4 (Figure 1) and grades 3 and 4 aGVHD was 26% (95% CI, 13 to 38), and only one patient developed grade 3 aGVHD (4%). No patients developed hyperacute GVHD. The median time to aGVHD diagnosis was 30 days (range, 16 to 72). The 2-year cumulative incidence of moderate-to-severe cGVHD was 16% (95% CI, 5 to 28). At the last follow-up, 81% of patients were off immunosuppressive treatment.

PFS, OS, and GRFS

The primary endpoint of the study was satisfied because the 1-year PFS was 60%. Furthermore, with the extended follow-up, the 4-year PFS was 54%, and the 4-year OS was 64% (Table 3, Figure 2). The 4-year GRFS was 52%. We performed a univariate analysis for PFS, OS, relapse, and NRM. Only recipient age (≥45 years) was predictive of lower OS (P = .016) (Table 4). Due to the low number of patients, a multivariate analysis was not performed.

Relapse Rate and NRM

The 4-year cumulative incidence of relapse was 28% (95% CI, 15% to 41%) (Table 3, Figure 3), and we did not observe further disease relapse after the second year. The median time from haploidentical stem cell transplantation (haplo-SCT) to relapse was 113 days (range, 18 to 387). Among the 15 relapsed patients, at the time of transplantation nine (60%)

Table 4
Univariate Analysis

	2-yr			
	PFS	OS	Relapse	NRM
Recipient age, n				
<45 yr	60	77	28	13
≥45 yr	45	50	27	27
P	.182	.016	.977	.088
Donor age, n				
<45 yr	48	65	33	19
≥45 yr	65	65	18	18
P	.444	.724	.234	.838
Disease status at transplant, n				
CR	55	72	21	24
PR/SD	52	57	35	13
P	.696	.197	.356	.515
Histology, n				
HL	62	67	17	21
NHL	46	63	38	17
P	.202	.574	.122	.946
HCTC-CI, n				
0–2	53	70	31	16
≥3	56	56	22	22
P	.918	.243	.517	.459
CMV serostatus (donor/recipient), n				
Any/– (0)	64	82	27	9
Other combinations	51	60	27	21
P	.562	.21	.953	.453
Sex mismatch (donor/recipient)				
Female/male	44	58	22	33
P	.928	.957	.69	.677
Donor kinship, n				
Child	46	46	23	31
Parents	70	80	20	10
Sibling	52	69	33	15
P	.594	.146	.653	.331
ABO incompatibility, n				
Major	57	71	14	28
Minor	55	55	36	9
None	52	66	28	20
P	.994	.773	.609	.481

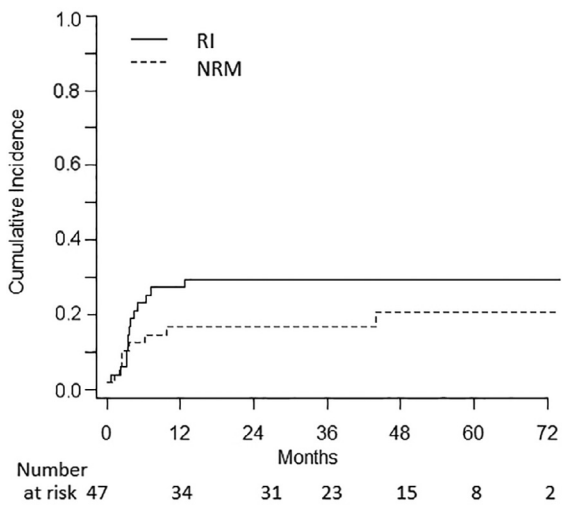

Figure 2. Survival for the entire population.

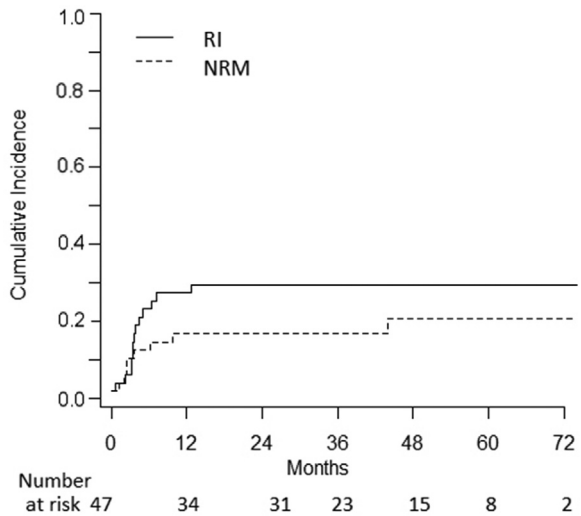

Figure 3. Relapse and NRM.

Table 5
Severe Extra-Hematological Toxicities

	Patients (n)	Description
Liver	6	Sinusoidal obstruction syndrome (1), transaminitis (5)
Mucosal	5	Mucositis (5)
Cardiac	4	Heart failure (3), pericardial tamponade (1)
Lung	3	Lung failure (2), pulmonary air embolism (1)
Kidney	2	Renal failure (1), urinary retention (1)
Central nervous system	1	Hemorrhage
PTLD	1	—
Psychological	1	Confusion
Endothelial	1	Transplantation-associated thrombotic microangiopathy
Other	4	—

PTLD indicates post-transplant lymphoprolipherative disease.

were in PR (60%), and six were in CR (40%). The 4-year NRM was 15% (range, 6% to 31%) (Table 3, Figure 2). The cause of death was disease progression in eight patients and toxicity in 10 patients.

Extrahematological Toxicities

Extrahematological toxicity for grades 3 and 4 was recorded in 40% of patients, mostly grade 3 (80%). As reported in Table 5, the most frequent type was liver toxicity, although only one patient developed sinusoidal obstruction syndrome (SOS), followed by cardiac toxicity, with three patients developing heart failure.

Infectious Complications

Cytomegalovirus (CMV) reactivation was analyzed in 42 patients (five donor/recipient pairs were negative/negative). The 1-year cumulative incidence of CMV reactivation was 57% (95% CI, 43% to 72%), and CMV-related disease was detected in two patients (colitis and pneumonia). The 1-year cumulative incidence of BK virus hemorrhagic cystitis was 28% (95% CI, 15% to 41%). The 1-year cumulative incidence of proven/probable invasive aspergillosis was 8.5% (95% CI, 4% to 17%). The 1-year cumulative incidence of bacterial infections was 34% (95% CI, 20% to 48%).

CONCLUSIONS

This prospective multicenter phase II study showed that in lymphomas with a poor prognosis, haploidentical bone marrow transplantation with an RIC regimen and PT-Cy was effective without excessive toxicity. The primary endpoint of the study was the 1-year PFS, which was 60%. With a longer follow-up, the 4-year PFS was stable (54%). The 4-year OS, relapse incidence, and NRM were 64%, 28%, and 15%, respectively.

The disease-related inclusion criteria were identical to those of a previous prospective study from the GITMO [5]. We are aware that the patient population included in this trial may not be representative of currently treated patients, as more recently some effective new drugs, which were not widely available when this study was conceived (in 2013), have been integrated into clinical practice. With this caveat, most of the patients had relapsed after previous high-dose chemotherapy or several lines of chemotherapy and can thus be considered to have an advanced and refractory disease.

The impact of the intensity of the conditioning regimen before allo-SCT in lymphoma patients is unknown. A prospective study, including only MRDs and MUDs, of patients conditioned by an NMAC regimen and peritransplant rituximab, reported an excellent survival rate (2-year event-free survival of 72% and OS of 78%) and low toxicity (2-year NRM of 13%), mainly in patients with chemosensitive disease [9]. Another prospective study including only patients with B cell lymphoma was published some years ago by Kanakry et al. [10], in which donor selection was based on the polymorphism of the rituximab Fc receptor. Most of the patients received unmanipulated bone marrow haplo-SCT (83%), and all patients were conditioned with the NMAC regimen and received prophylactic PT-Cy. Weekly rituximab was added starting at day +30 for 8 weeks. In the group of patients receiving haplo-SCT, the 1-year PFS, OS, relapse rate, and NRM were 70%, 83%, 20%, and 10%, respectively. In other studies, not including haploidentical donors, the use of a more intensive conditioning regimen did not result in a clear advantage in survival [11-15]. Last, a recent publication from the Center for International Blood and Marrow Transplant Research reported that, in transplantations involving MRDs and MUDs, more intensive melphalan-based RIC regimens were more toxic than other regimens, including cyclophosphamide or busulfan or low-dose TBI. Furthermore, OS was also lower after melphalan-based RIC [16].

The conditioning regimen used in the present study was inspired by the GITMO study published several years ago, which included only MRDs and MUDs, and it was considered to be active against lymphoid malignancies. We modified this regimen by adding low-dose (2 Gy) TBI or TMI/TLI to reduce the risk of graft failure. This was indeed the case, as only one patient developed primary graft failure. However, considering the experience in recent years using RIC regimens without low-dose TBI, mainly incorporating thiotepa, busulfan, and fludarabine [17], the addition of TBI could probably be avoided, thus reducing the risk of secondary neoplasia, as was recently reported [18]. Compared with the previous GITMO study [5], although the 3-year NRM was similar (14% versus 15% in our study), we observed a striking difference in terms of aGVHD and cGVHD, as the cumulative incidence of grades 2 to 4 aGVHD in the GITMO study was 35%, compared with 26% in our study, and the cumulative incidence of cGVHD was 52%, compared to 21% in our study. There are at least two possible explanations for these differences. First, in the GITMO study, peripheral blood stem cells (PBSCs) were used as a stem cell source, and it is well known that the risk of GVHD is higher in PBSC-based transplantations than in bone marrow stem-cell-based transplantations [19]. Second, PT-Cy as GVHD prophylaxis has been reported to reduce the incidence of severe aGVHD [20], especially cGVHD [21].

The relapse rate in our study was 28% at 3 years. This endpoint can be acceptable and seems to be lower than that in other series using truly nonmyeloablative conditioning regimens [22,23]. However, although it is always difficult to compare different studies with differences in patient populations, the intensity of the conditioning regimen could provide a reasonable explanation for this finding. Indeed, in our study, only patients with well-controlled disease before transplantation were included, leading to a positive selection bias.

In our study, we used bone marrow as a stem cell source, and, as discussed above, this can partially explain the low incidence of GVHD. However, in recent years, many reports have been published on the use of PBSCs [24], and two retrospective comparative studies confirmed that the cumulative incidence of aGVHD and cGVHD was higher with PBSCs [25,26].

Nonetheless, there were no effects, in either study, on NRM or survival.

Overall, the toxicity profile observed in this study was acceptable: grade 3 and 4 toxicity was observed in 40% of patients and was mainly grade 3. In this heavily pretreated population, liver toxicity was frequent, but only one patient developed SOS. Four patients showed cardiac complications, and, notably, three of them had heart failure, which could be due to cyclophosphamide. No clear association between cyclophosphamide and heart toxicity has been reported in the literature, and in one study posttransplantation cardiomyopathy was linked to infectious complications rather than drug toxicity [27]. However, we reduced the dose of cyclophosphamide in the conditioning regimen (from 60 mg/kg to 30 mg/kg) to avoid excessive cardiac toxicity.

The infectious complications in this study were quite similar to those previously reported [28]. Viral infections were common; in particular, 57% of patients experienced CMV reactivation, although the incidence of CMV-related disease was low. Other viral infections, such as BK virus hemorrhagic cystitis, were less frequent. The cumulative incidence of invasive fungal infections was 8.5%, similar to the finding of a previous report [29]. The 1- and 3-year NRM rates were both 15%, which is not very different from the values reported in a prospective study in lymphoma patients using NMAC [22,23]. The low mortality rate is another key finding, considering that RIC regimens are associated with a higher mortality in heavily pretreated patients [14].

In conclusion, this prospective multicenter study demonstrated that a RIC regimen before haplo-SCT was well tolerated with a low incidence of GVHD and low NRM. The survival is encouraging, with a plateau after the first 2 years after transplantation.

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