Biol Blood Marrow Transplant 25 (2019) 1803–1809

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Thiotepa, Fludarabine, and Busulfan Conditioning Regimen before T Cell–Replete Haploidentical Transplantation with Post-Transplant Cyclophosphamide for Acute Myeloid Leukemia: A Bicentric Experience of 100 Patients

Thomas Pagliardini[1], Lucas Castagna[2], Samia Harbi[1], Matteo Della Porta[2], Jerome Rey[1], Sabine Fürst[1], Stefania Bramanti[2], Colombe Saillard[1], Faezeh Legrand[1], Valerio Maisano[1], Catherine Faucher[1], Angela Granata[1], Marie-Anne Hospital[1], Wang Lining[3], Pierre-Jean Weiller[1], Boris Calmels[4], Aude Charbonnier[1], Claude Lemarie[4], Christian Chabannon[4,5,6,7], Norbert Vey[1,5,6], Djamel Mokart[8], Didier Blaise[1,5,6], Raynier Devillier[1,5,6,*]

[1] *Department of Hematology, Institut Paoli-Calmettes, Marseille, France*
[2] *Department of Hematology, Humanitas Cancer Center, Rozzano, Italy*
[3] *Department of Hematology, Shanghai Institute of Hematology, Shanghai, China*
[4] *Centre de Thérapie Cellulaire, Institut Paoli-Calmettes, Marseille, France*
[5] *Centre de Recherche en Cancérologie de Marseille, Inserm U1068, UMR 7258, Marseille, France*
[6] *Aix-Marseille University, UM 105, Marseille, France*
[7] *CIC Biothérapies, Inserm CBT-1409, Marseille, France*
[8] *Intensive Care Unit, Institut Paoli-Calmettes, Marseille, France*

Article history:
Received 11 February 2019
Accepted 12 May 2019

Keywords:
Thiotepa-busulfan-fludarabine
Haploidentical SCT
AML

A B S T R A C T

Haploidentical stem cell transplantation (haplo-SCT) with post-transplant cyclophosphamide (PT-Cy) is an alternative treatment for acute myeloid leukemia (AML) patients who lack HLA-matched donors. Relapse after haplo-SCT remains a major concern, especially after nonmyeloablative conditioning regimens. Promising results were reported for TBF-based conditioning regimens (thiotepa, busulfan, and fludarabine) in patients transplanted from different categories of donors and for various disease types but not specifically in PT-Cy haplo-SCT for AML. Here we evaluate the outcome of 100 AML patients who received haplo-SCT with PT-Cy after TBF conditioning regimens (reduced-intensity conditioning, n = 77; myeloablative conditioning, n = 23) in 2 transplant programs. Cumulative incidences of grades III to IV acute and moderate or severe chronic graft-versus-host disease (GVHD) were 7% and 14%, respectively. NRM at 2 years was 28%, significantly influenced by disease status at haplo-SCT (first complete response [CR1] versus advanced AML: 16% versus 38%, $P = .016$) but not by conditioning intensity or age. The cumulative incidences of relapse at 2 years were 17% and 24% in CR1 and advanced AML, respectively (not significant). Progression-free survival, overall survival, and GVHD and relapse-free survival at 2 years were 67%, 71%, and 49% in CR1 patients, respectively, whereas comparative values in patients with advanced disease were 37%, 41%, and 32%. Our study suggests that TBF conditioning for PT-Cy haplo-SCT is safe and effective for AML patients in CR1. In patients with more advanced disease, the relatively low incidence of relapse seems counterbalanced by a high nonrelapse mortality, underlining the need for alternative strategies to decrease relapse risk, without increasing the intensity of conditioning regimen.

INTRODUCTION

Haploidentical hematopoietic stem cell transplantation (haplo-SCT) with post-transplant cyclophosphamide (PT-Cy) results in low rates of both graft-versus-host disease (GVHD) and nonrelapse mortality (NRM) using a nonmyeloablative conditioning (NMAC) regimen (Cy 29 mg/kg, fludarabine 150 mg/m^2, and low-dose total body irradiation 2 Gy) [1]. However, the relapse rate remains a concern, especially for patients with myeloid malignancies. Indeed, previous reports of NMAC haplo-SCT for acute myeloid leukemia (AML) and/or myelodysplastic syndromes showed a cumulative incidence of relapse

Financial disclosure: See Acknowledgments on page 1808.
* Correspondence and reprint requests: Raynier Devillier, MD, PhD, Hematology Department, Institut Paoli Calmettes, 232 boulevard Sainte Marguerite, Marseille, France.
E-mail address: devillierr@ipc.unicancer.fr (R. Devillier).

https://doi.org/10.1016/j.bbmt.2019.05.014
1083-8791/

from 45% [1,2] to 58% [3,4]. In the setting of HLA-identical transplantation, we and others previously reported the benefit in disease control using more intensive regimens, most of them containing busulfan [5-10].

In the context of haplo-SCT, the role of conditioning regimen intensity on leukemic control after PT-Cy haplo-SCT remains a matter of debate, specifically for AML patients [11-16]. The association of thiotepa, busulfan, and fludarabine (TBF) in different dose combinations showed promising results for various situations of donor and disease types [17-19]. However, data are missing for TBF conditioning regimens in the specific setting of haplo-SCT with PT-Cy for AML patients. Here we report the results of a retrospective analysis of AML patients who received haplo-SCT conditioned with TBF plus PT-Cy at 2 European transplant programs.

METHODS

Selection Criteria

Inclusion criteria were as follows: adult patients with AML according to World Health Organization criteria [20], undergoing haplo-SCT with PT-Cy between January 2011 and June 2018 in 2 collaborative transplant centers (Paoli Calmettes Institute of Marseille and Humanitas Cancer Center of Milan), and using a TBF conditioning regimen. All patients signed informed consent for data collection and participation in this retrospective database analysis.

Conditioning Regimen and GVHD Prophylaxis

Fludarabine total dose was 120 to 160 mg/m^2 whatever the conditioning intensity. The European Society for Blood and Marrow Transplantation criteria were used to define reduced-intensity conditioning (RIC; i.v. busulfan total dose $\leq$ 260 mg/m^2) and myeloablative conditioning (MAC; i.v. busulfan total dose $>$ 260 mg/m^2) regimens. TBF-RIC was defined as the association of thiotepa (5 mg/kg/day for 1 day), fludarabine (30 to 40 mg/m^2/day for 4 days), and i.v. busulfan (130 mg/m^2/day for 2 days). TBF-MAC included more intensive combinations of thiotepa (5 mg/kg/day for 1 or 2 days), fludarabine (30 to 40 mg/m^2/day for 4 days), and i.v. busulfan (130 mg/m^2/day for 3 or 4 days). We did not use pharmacokinetic dosages of busulfan. GVHD prophylaxis was based on PT-Cy (50 mg/kg on days +3 and +4) and cyclosporine A plus mycophenolate mofetil starting on day +5 [1,21].

Statistical Analyses

Times to events were calculated from the date of haplo-SCT, and patients were censored at last contact in the absence of a relevant event. Glucksberg and National Institutes of Health classifications were used for the gradation of acute and chronic GVHD, respectively [22,23]. The Prentice estimate [24] and Gray test [25] considering competing events were used to calculate the cumulative incidences of GVHD, NRM, and cumulative incidence of relapse (CIR). NRM and relapse were considered as mutually competing events. To calculate the cumulative incidence of GVHD, death from any cause before the occurrence of GVHD was considered as a competing event. The Kaplan-Meier method and log rank test were used for OS, progression-free survival (PFS), and GVHD and relapse-free survival (GRFS) analyses [26]. Relevant events for GRFS were relapse, death from any cause, and occurrence of grades III and IV acute and moderate or severe chronic GVHD [27,28].

By univariate and multivariate analyses we evaluated the impact of age ($<$60 versus $\geq$60 years), hematopoietic cell transplantation–specific comorbidity index (HCT-CI) [29] ($<$3 versus $\geq$3), disease status at the time of haplo-SCT (first complete response [CR1] versus advanced AML), conditioning intensity (RIC versus MAC), and cytogenetic risk group (low/intermediate versus high risk). A multivariate Cox model was performed to compute the proportional hazard ratio [30]. All survival analyses were computed using R 3.5.3 statistical software (http://www.R-project.org).

RESULTS

Patient and Transplant Characteristics

One hundred consecutive patients with a median age of 58 years (range, 22 to 72) were analyzed (Table 1). Forty-nine patients were transplanted in CR1, whereas the 51 remaining patients were transplanted in subsequent CR (CR $>$ 1, n = 35) or with refractory disease (n = 16). Because of the low number of patients with refractory disease and the absence of significant difference for all endpoints between patients transplanted for advanced AML (Supplementary Table S1), we pooled those patients in the advanced disease group for the following analyses. Twenty-seven (17 in CR1), 73 (32 in CR1), and 6 (1 in CR1) patients had unfavorable, intermediate, and favorable cytogenetics, respectively. HCT-CI was $\geq$3 in 63 patients (30/49 [61%] and 33/51 [64%] in the CR1 and advanced disease groups, respectively). Most patients received TBF-RIC regimens (n = 77) and peripheral blood stem cells as graft source (n = 85). In CR1 patients, 39 of 49 patients (80%) and 10 of 49 patients (20%) received TBF-RIC and TBF-MAC, respectively. Twelve patients had previous allogeneic transplantation. Median follow-up after haplo-SCT was 25 months (range, 4 to 62).

Table 1
Patient and Transplant Characteristics (N = 100)

Characteristic	Value
Age, yr, median (min-max)	58 (22-72)
Gender	
Male	59
Female	41
HCT-CI score	
$<$3	37
$\geq$3	63
Cytomegalovirus serostatus donor/recipient	
−/−	15
−/+	34
+/−	2
+/+	49
Cytogenetic	
Favorable	6
Intermediate	67
Unfavorable	27
Disease status at haplo-SCT	
CR1	49
CR $>$ 1	35
Refractory AML	16
No. of haplo-SCTs by year	
2011	3
2012	4
2013	10
2014	7
2015	20
2016	31
2017	19
2018	6
Allo-SCT	
First	88
Second	12
Conditioning regimen	
TBF-RIC	77
TBF-MAC	23
Stem cell source	
Bone marrow	15
Peripheral blood stem cell	85
CD34$^+$, 10^6/kg, median (min-max)	5.1 (1.4-16.1)

Engraftment

Five patients died before hematologic recovery from infectious complications and thus were not assessable for engraftment (deaths between days +4 and +16). All 95 remaining patients achieved full donor chimerism (74 before day 45 and 21 after day 45). Median time from haplo-SCT to neutrophil ($>$.5

Table 2
Univariate Comparison for NRM, CIR, PFS, OS, and GRFS after Haplo-SCT

		NRM			CIR			PFS			OS			GRFS		
	No. of Cases	Percent	95% CI	*P*	Percent	95% CI	*P*	Percent	95% CI	*P*	Percent	95% CI	*P*	Percent	95% CI	*P*
Age																
<60 yr	51	28	14-40	.878	20	8-31	.908	51	39-68	.841	56	44-73	.771	39	27-55	.823
≥60 yr	49	27	13-38		21	8-32		53	40-69		55	43-72		42	30-59	
HCT-CI score																
<3	37	14	2-24	.025	22	7-35	.458	64	50-82	.143	69	55-86	.053	55	41-74	.048
≥3	63	36	22-47		20	9-29		45	34-59		48	37-63		32	22-46	
Cytogenetic																
Favorable/intermediate	73	27	16-37	.831	17	8-25	.282	56	45-68	.511	59	48-72	.355	43	32-56	.777
Unfavorable	27	28	8-44		31	11-47		41	25-66		46	30-72		33	19-58	
Disease status																
CR1	49	16	5-26	.016	17	5-27	.258	67	55-82	.001	71	59-86	.006	49	36-66	.013
Advanced AML	51	38	23-51		24	11-35		37	26-54		41	29-58		32	21-48	
Conditioning regimen																
TBF-RIC	77	29	18-39	.552	21	11-30	.665	50	39-62	.398	52	42-65	.461	36	27-49	.134
TBF-MAC	23	23	3-39		18	0-33		59	41-84		67	49-91		54	36-80	

All estimations are given at 2 years after haplo-SCT. CI indicates confidence interval.

Giga/liter) and platelet (>20 Giga/liter) recovery was 23 (range, 6 to 112) and 28 (range, 6 to 220) days, respectively. Three patients had delayed neutrophil recovery (beyond day +35) on days +37, +45, and +112 because of infectious complications.

Graft-versus-Host Disease

In the entire cohort, the cumulative incidences of grades II to IV and III to IV acute GVHD at day 100 were 23% and 7%, respectively. At 2 years after haplo-SCT, the cumulative incidences of all grades and moderate chronic GVHD were 25% and 14%, respectively. No patient developed severe chronic GVHD. Univariate comparisons did not reveal significant risk factors for the development of both acute and chronic GVHD (Supplementary Table S2). Multivariate analysis did not identify any predictive factor of GVHD.

Nonrelapse Mortality

The cumulative incidence of NRM at 2 years after haplo-SCT was 28% in the whole cohort. We observed that patients transplanted in CR1 had significantly lower NRM compared with those transplanted for advanced AML (2-year NRM: CR1 versus advanced AML, 16% versus 38%, $P = .016$) (Table 2, Figure 1A). HCT-CI ≥ 3 was associated with a significantly higher incidence of NRM (2-year NRM: <3 versus ≥3, 14% versus 36%, $P = .025$) (Table 2, Figure 1B). By contrast, age and conditioning intensity did not significantly influence NRM in univariate analyses. Multivariate analysis confirmed a higher risk of NRM in patients with HCT-CI ≥ 3 (hazard ratio [HR], 2.81; $P = .040$) and in patients transplanted for advanced AML (HR, 3.31; $P = .008$) (Table 3). Causes of NRM were infectious complications (n = 16, 60%), GVHD (n = 7, 26%), 2 neurologic failures, 1 heart failure, and 1 secondary cancer.

Cytomegalovirus and Epstein-Barr Virus Reactivations

Sixty-one patients developed cytomegalovirus viremia. Among them, 32 were in CR1 and 29 were transplanted for advanced AML. Epstein-Barr Virus viremia occurred in 6 patients, and no post-transplant lymphoproliferative disease was observed.

Relapse

CIR at 2 years was 21% in the entire cohort, without significant differences associated with disease status at the time of haplo-SCT (CR1 versus advanced AML, 17% versus 24%; $P = .258$) (Table 2). In addition, we did not observe a significant decrease in 2-year CIR using TBF-MAC compared with TBF-RIC, 18% versus 21% ($P = .665$), respectively. The 2-year CIRs were 17% and 31% in low/intermediate and unfavorable cytogenetic risk groups ($P = .282$), respectively. In multivariate analysis, advanced AML was associated with a higher risk of relapse (HR, 2.54; $P = .041$) (Table 3).

Survivals

In the entire cohort 2-year PFS, OS, and GRFS were 52%, 56%, and 40%, respectively. Outcome of CR1 patients was significantly better compared with those transplanted for advanced AML (PFS: 67% versus 37%, $P = .001$ [Figure 2A]; OS: 71% versus 46%, $P = .006$; GRFS: 49% versus 32%, $P = 0.013$) (Table 2). HCT-CI ≥ 3 was associated with a significantly lower 2-year GRFS (<3 versus ≥3: 55% versus 32%, $P = .048$) (Table 2), a trend for lower 2-year OS (<3 versus ≥3: 69% versus 48%, $P = .053$) (Table 2), and no significant difference in 2-year PFS (<3 versus ≥3: 64% versus 45%, $P = .143$) (Table 2, Figure 2B). Age and conditioning intensity did not influence any survival endpoints in univariate analyses. Multivariate analysis

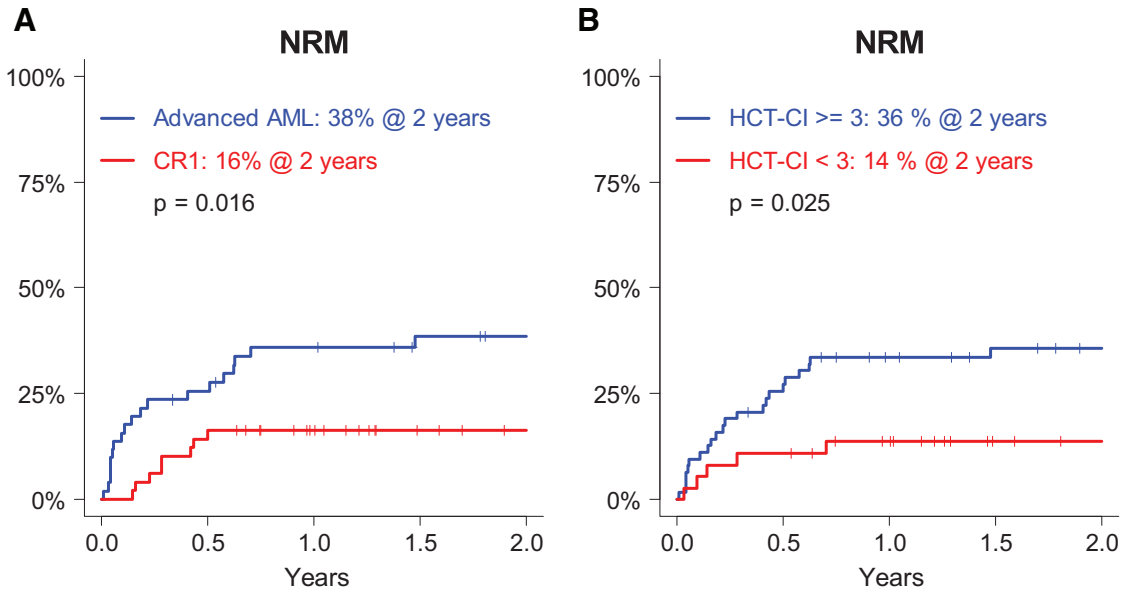

Figure 1. NRM according to disease status at the time of haplo-SCT (A) and HCT-CI (B).

confirmed that PFS, OS, and GRFS were significantly better for patients transplanted in CR1 (advanced AML) (OS: HR, 2.69 [$P = .004$]; PFS: HR, 2.71 [$P = .002$]; GRFS: HR, 1.98 [$P = .014$]) (Table 3). Moreover, we did not observe any significant impact of age or conditioning intensity on OS, PFS, and GRFS, whereas we observed trends for worse OS in patients with HCT-CI ≥ 3 (HR, 1.78; $P = .091$) and in patients with unfavorable cytogenetics (HR, 1.93; $P = .062$) (Table 3).

DISCUSSION

The use of a haploidentical donor strongly improves the feasibility of allogeneic transplant because it virtually allows identifying at least 1 donor for every candidate for allogeneic HSCT. The use of PT-Cy as part of GVHD prophylaxis is associated with in vivo depletion of alloreactive lymphocytes and low incidences of GVHD, resulting in survival rates that approach those observed after HLA-matched related or unrelated donor transplants. In the setting of AML, disease recurrence after haplo-SCT remains a major concern, however, especially when a NMAC regimen is used (45% to 58%) [1-4]. The use of more intensive regimens has been reported for different clinical situations [15,17,31], including AML [11-14,16,32], but to our knowledge no study specifically evaluated the feasibility and efficacy of TBF regimens for haplo-SCT in AML patients.

Thus, we analyzed the first 100 consecutive patients to receive TBF conditioning regimens before haplo-SCT with PT-Cy from 2 collaborating centers. All patients received the same GVHD prophylaxis and conditioning therapy (although doses can vary), contributing to a certain degree of homogeneity. We observed low incidences of severe forms of acute (grades III to IV, 7%) and chronic (moderate, 14%; severe, 0%) GVHD despite the high proportion of patients (85%) who were given peripheral blood stem cells as graft source. These incidences seemed lower than previously reported results of peripheral blood stem cell

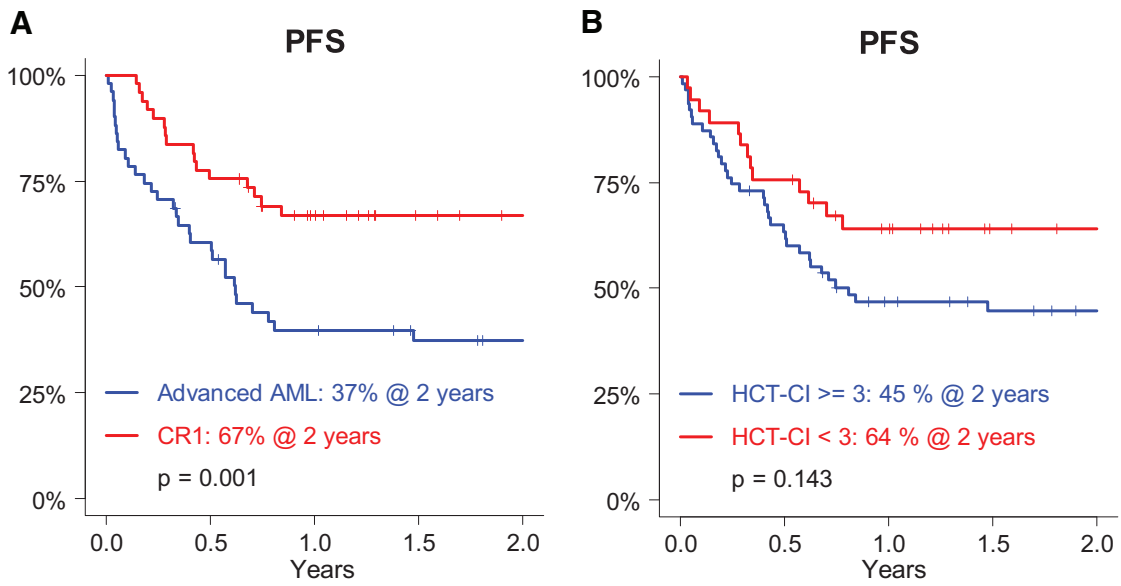

Figure 2. PFS according to disease status at the time of haplo-SCT (A) and HCT-CI (B).

Table 3
Multivariate Cox Model

	Age (continuous)			RIC vs. MAC			Unfavorable vs. Intermediate/Favorable			HCT-CI ≥ 3 vs. <3			Advanced AML vs. CR1		
	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Grades II-IV acute GVHD	1.00	.97-1.04	.846	1.25	.45-3.46	.667	1.26	.51-3.15	.617	.94	.42-2.09	.883	.73	.31-1.68	.457
All grades chronic GVHD	.99	.95-1.03	.581	2.34	.74-7.34	.146	1.79	.61-5.27	.292	2.36	.92-6.05	.074	1.47	.59-3.70	.411
NRM	1.02	.98-1.06	.313	1.18	.43-3.27	.749	1.45	.58-3.65	.427	2.81	1.05-7.53	.040	3.31	1.38-7.98	.008
Relapse	.98	.95-1.01	.204	1.76	.62-4.94	.286	2.13	.82-5.50	.119	.72	.31-1.68	.449	2.54	1.04-6.21	.041
PFS	1.00	.98-1.02	.918	1.47	.71-3.03	.295	1.71	.89-3.30	.109	1.38	.74-2.55	.307	2.71	1.46-5.03	.002
OS	1.01	.98-1.03	.613	1.37	.63-2.95	.426	1.93	.97-3.84	.062	1.78	.91-3.49	.091	2.69	1.38-5.23	.004
GRFS	1.00	.98-1.02	.957	1.76	.89-3.47	.106	1.47	.80-2.69	.216	1.56	.89-2.73	.122	1.98	1.15-3.43	.014

haplo-SCT [11,33,34] and are more comparable with that observed using bone marrow grafts [21,34,35]. However, the relative heterogeneity in patient and transplantation characteristics across these studies limits the possibility of comparison.

We separately analyzed patients transplanted in CR1 and those transplanted for more advanced disease (advanced AML) because it is a major determinant of outcome. In CR1 patients, a TBF conditioning regimen is well tolerated, with similar a NRM rate (16%) compared with previously reported NRM data after either NMAC (9% to 15%) [1,3,4] or more intensive conditioning regimens (13% to 30%) [15,16]. This underlines the difficulty to retrospectively assess the impact of conditioning intensity in a homogeneous disease-specific context. In addition, the CIR in CR1 patients was relatively low (17%) despite 35% of them having unfavorable cytogenetics. As for comparison, the CIR at 2 years was about 50% after NMAC [1,3] and 19% to 40% after MAC experiences [11-14,17,32]. We thus suggest that the TBF regimen is a feasible conditioning platform for CR1 AML patients, producing promising outcome (OS, 71%) after haplo-SCT. In patients with more advanced disease features (CR > 1/refractory disease, eventually after a first allogeneic transplant), the 2-year CIR of 24% is encouraging but is counterbalanced by the high incidence of NRM, mostly because of severe bacterial infections rather than GVHD. We also observed 61% of cytomegalovirus viremia that is comparable with previous reports in the setting of haplo-SCT (75%) [36] but higher than our previous experience of matched related or unrelated donor transplant before 2011 (35%) [37]. Altogether, our results underline the frailty of these patients, possibly related to the cumulative toxicity of previous treatments. Thus, we suggest that a TBF regimen should be used with caution in this high-risk population, the benefit of the antitumor effect being counterbalanced by an increase in NRM, especially if HCT-CI is high. Strategies to better select patients for intensification and optimization of anti-infectious prophylaxis are needed in this context. In addition, the use of pharmacokinetic data for busulfan dose adjustment could improve the safety of this platform [38]. Moreover, post-transplant treatments such as tyrosine kinase inhibitors [39,40] and/or donor lymphocyte infusions [41,42] could be helpful to overcome in part the high risk of relapse in this advanced disease population when intensifying the conditioning regimen is not feasible.

The strength of our study is that transplant procedures are relatively homogeneous across both centers, with similar GVHD prophylaxis. The main weakness of our study is its retrospective nature. Although the analysis of 100 patients seems sufficient to observe trends, we were not able to perform subgroup analyses because of the relatively low number of patients in each group. Thus, some confounding factors such as previous allogeneic transplant or disease status at the time of haplo-SCT are strong limitations for interpreting the data in the entire cohort. To deal with this issue, we separately analyzed CR1 and advanced AML patients, leading to different conclusions based on that criteria. However, the low number of patients who received TBF-MAC did not allow us to separately explore the role of conditioning intensity across these disease risk subgroups.

We conclude that a TBF platform for haplo-SCT with PT-Cy is suitable for AML patients, with high antileukemic activity in both CR1 and advanced disease groups. Although no excess of NRM was observed in CR1 patients—encouraging haplo-SCT in CR1 AML—the TBF platform should be used with caution in patients with advanced AML, with higher NRM counterbalancing the benefit in disease control. Optimized selection and transplantation procedures are still specifically needed for high-risk patients.

ACKNOWLEDGMENTS

The authors thank patients and the hematology staff from both centers.

Financial disclosure: The authors have nothing to disclose.

Conflict of interest statement: There are no conflicts of interest to report.

Authorship statement: D.B. and R.D. are co–senior authors. T.P., L.C., D.B., and R.D. contributed to patient care, designed the study, collected and analyzed data, and wrote the manuscript. R.D. and T.P. performed statistical analyses. S.H., J.R., S.F., S.B., F.L., V.M., C.F., A.G., L.W., P.J.W., N.V., and D.M. contributed to patient care and data collection. B.C., C.L., and C.C. supervised donor search, cell collection, cell processing, and related data collection. All authors read and approved the manuscript.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at doi:10.1016/j.bbmt.2019.05.014.

REFERENCES

1. Luznik L, O'Donnell PV, Symons HJ, et al. HLA-haploidentical bone marrow transplantation for hematologic malignancies using nonmyeloablative conditioning and high-dose, posttransplantation cyclophosphamide. *Biol Blood Marrow Transplant*. 2008;14:641–650.
2. Brunstein CG, Fuchs EJ, Carter SL, et al. Alternative donor transplantation after reduced intensity conditioning: results of parallel phase 2 trials using partially HLA-mismatched related bone marrow or unrelated double umbilical cord blood grafts. *Blood*. 2011;118:282–288.
3. McCurdy SR, Kanakry JA, Showel MM, et al. Risk-stratified outcomes of nonmyeloablative HLA-haploidentical BMT with high-dose posttransplantation cyclophosphamide. *Blood*. 2015;125:3024–3031.
4. Ciurea SO, Zhang M-J, Bacigalupo AA, et al. Haploidentical transplant with post-transplant cyclophosphamide versus matched unrelated donor transplant for acute myeloid leukemia. *Blood*. 2015;126:1033–1040.
5. Blaise D, Tabrizi R, Boher J-M, et al. Randomized study of 2 reduced-intensity conditioning strategies for human leukocyte antigen-matched, related allogeneic peripheral blood stem cell transplantation: prospective clinical and socioeconomic evaluation. *Cancer*. 2013;119:602–611.
6. Shimoni A, Hardan I, Shem-Tov N, et al. Allogeneic hematopoietic stem-cell transplantation in AML and MDS using myeloablative versus reduced-intensity conditioning: the role of dose intensity. *Leukemia*. 2006;20:322–328.
7. Oudin C, Chevallier P, Furst S, et al. Reduced-toxicity conditioning prior to allogeneic stem cell transplantation improves outcome in patients with myeloid malignancies. *Haematologica*. 2014;99:1762–1768.
8. De Lima M, Anagnostopoulos A, Munsell M, et al. Nonablative versus reduced-intensity conditioning regimens in the treatment of acute myeloid leukemia and high-risk myelodysplastic syndrome: dose is relevant for long-term disease control after allogeneic hematopoietic stem cell transplantation. *Blood*. 2004;104:865–872.
9. Bornhäuser M, Kienast J, Trenschel R, et al. Reduced-intensity conditioning versus standard conditioning before allogeneic haemopoietic cell transplantation in patients with acute myeloid leukaemia in first complete remission: a prospective, open-label randomised phase 3 trial. *Lancet Oncol*. 2012;13:1035–1044.
10. Ringdén O, Labopin M, Ehninger G, et al. Reduced Intensity Conditioning Compared With Myeloablative Conditioning Using Unrelated Donor Transplants in Patients With Acute Myeloid Leukemia. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2009;27:4570–4577.
11. Solomon SR, Sizemore CA, Sanacore M, et al. Haploidentical transplantation using T cell replete peripheral blood stem cells and myeloablative conditioning in patients with high-risk hematologic malignancies who lack conventional donors is well tolerated and produces excellent relapse-free survival: results of a prospective phase II trial. *Biol Blood Marrow Transplant*. 2012;18:1859–1866.
12. Pingali SR, Milton D, Stasi A di, et al. Haploidentical Transplantation for Advanced Hematologic Malignancies Using Melphalan-Based Conditioning – Mature Results from a Single Center. *Biology of Blood and Marrow Transplantation*. 2014;20:S40–S41.
13. Solomon SR, Sizemore CA, Sanacore M, et al. Total Body Irradiation–Based Myeloablative Haploidentical Stem Cell Transplantation Is a Safe and Effective Alternative to Unrelated Donor Transplantation in Patients Without Matched Sibling Donors. *Biology of Blood and Marrow Transplantation*. 2015;21:1299–1307.
14. Solomon SR, Solh M, Morris LE, Holland HK, Bashey A. Myeloablative Conditioning with PBSC Grafts for T Cell-Replete Haploidentical Donor Transplantation Using Posttransplant Cyclophosphamide. *Adv Hematol*. 2016;2016: 9736564.
15. Bacigalupo A, Dominietto A, Ghiso A, et al. Unmanipulated haploidentical bone marrow transplantation and post-transplant cyclophosphamide for hematologic malignanices following a myeloablative conditioning: an update. *Bone Marrow Transplant*. 2015;50:S37–S39.
16. Rubio MT, Savani BN, Labopin M, et al. Impact of conditioning intensity in T-replete haplo-identical stem cell transplantation for acute leukemia: a report from the acute leukemia working party of the EBMT. *J Hematol Oncol*. 2016;9:25.
17. Raiola AM, Dominietto A, Ghiso A, et al. Unmanipulated haploidentical bone marrow transplantation and posttransplantation cyclophosphamide for hematologic malignancies after myeloablative conditioning. *Biol Blood Marrow Transplant*. 2013;19:117–122.
18. Saraceni F, Labopin M, Hamladji R-M, et al. Thiotepa-busulfan-fludarabine compared to busulfan-fludarabine for sibling and unrelated donor transplant in acute myeloid leukemia in first remission. *Oncotarget*. 2018;9:3379–3393.
19. Saraceni F, Beohou E, Labopin M, et al. Thiotepa, busulfan and fludarabine compared to busulfan and cyclophosphamide as conditioning regimen for allogeneic stem cell transplant from matched siblings and unrelated donors for acute myeloid leukemia. *Am J Hematol*. 2018;93:1211–1219.
20. Döhner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. *Blood*. 2017;129:424–447.
21. Castagna L, Crocchiolo R, Furst S, et al. Bone Marrow Compared with Peripheral Blood Stem Cells for Haploidentical Transplantation with a Nonmyeloablative Conditioning Regimen and Post-transplantation Cyclophosphamide. *Biology of Blood and Marrow Transplantation*. 2014;20:724–729.
22. Jagasia MH, Greinix HT, Arora M, et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. The 2014 Diagnosis and Staging Working Group report. *Biol Blood Marrow Transplant*. 2015;21:389–401.
23. Przepiorka D, Weisdorf D, Martin P, et al. 1994 Consensus Conference on Acute GVHD Grading. *Bone Marrow Transplant*. 1995;15:825–828.
24. Prentice RL, Kalbfleisch JD, Peterson AV, Flournoy N, Farewell VT, Breslow NE. The analysis of failure times in the presence of competing risks. *Biometrics*. 1978;34:541–554.
25. Gray RJ. A class of K-sample tests for comparing the cumulative incidence of a competing risk. *The Annals of statistics*. 1988;16:1141–1154.
26. Kaplan EL, Meier P. Nonparametric Estimation from Incomplete Observations. *Journal of the American Statistical Association*. 1958;53:457.
27. Holtan SG, DeFor TE, Lazaryan A, et al. Composite end point of graft-versus-host disease-free, relapse-free survival after allogeneic hematopoietic cell transplantation. *Blood*. 2015;125:1333–1338.
28. Ruggeri A, Labopin M, Ciceri F, Mohty M, Nagler A. Definition of GvHD-free, relapse-free survival for registry-based studies: an ALWP-EBMT analysis on patients with AML in remission. *Bone Marrow Transplant*. 2016;51:610–611.
29. Sorror ML, Maris MB, Storb R, et al. Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. *Blood*. 2005;106:2912–2919.
30. Cox D. Regression models and life tables. *Journal of the Royal Statistical Society: Serie B (Methodological)*. 1972;34:187–220.
31. Cieri N, Greco R, Crucitti L, et al. Post-transplantation Cyclophosphamide and Sirolimus after Haploidentical Hematopoietic Stem Cell Transplantation Using a Treosulfan-based Myeloablative Conditioning and Peripheral Blood Stem Cells. *Biology of Blood and Marrow Transplantation*. 2015;21:1506–1514.
32. Gayoso J, Balsalobre P, Kwon M, et al. Myeloablative Conditioning Haploidentical Stem Cell Transplantation (MAC-HAPLO) with Post-Transplant Cyclophosphamide (PTCy) As GvHD Prophylaxis in High Risk Leukemias/Myelosdysplastic Syndromes (MDS): Geth Experience. *Blood*. 2016;128:4690.
33. Ruggeri A, Labopin M, Bacigalupo A, et al. Bone marrow versus mobilized peripheral blood stem cells in haploidentical transplants using posttransplantation cyclophosphamide. *Cancer*. 2018;124:1428–1437.
34. Bashey A, Zhang M-J, McCurdy SR, et al. Mobilized Peripheral Blood Stem Cells Versus Unstimulated Bone Marrow As a Graft Source for T-Cell-Replete Haploidentical Donor Transplantation Using Post-Transplant Cyclophosphamide. *J Clin Oncol*. 2017;35:3002–3009.
35. O'Donnell PV, Eapen M, Horowitz MM, et al. Comparable outcomes with marrow or peripheral blood as stem cell sources for hematopoietic cell transplantation from haploidentical donors after non-ablative conditioning: A matched-pair analysis. *Bone marrow transplantation*. 2016;51:1599.
36. Slade M, Goldsmith S, Romee R, et al. Epidemiology of infections following haploidentical peripheral blood hematopoietic cell transplantation. *Transpl Infect Dis*. 2017;19:12629.
37. Venton G, Crocchiolo R, Fürst S, et al. Risk factors of Ganciclovir-related neutropenia after allogeneic stem cell transplantation: a retrospective monocentre study on 547 patients. *Clin Microbiol Infect*. 2014;20:160–166.

38. Andersson BS, Thall PF, Valdez BC, et al. Fludarabine with pharmacokinetically guided IV busulfan is superior to fixed-dose delivery in pretransplant conditioning of AML/MDS patients. *Bone Marrow Transplant*. 2017;52:580–587.
39. Freitas TD, Marktel S, Piemontese S, et al. High rate of hematological responses to sorafenib in FLT3-ITD acute myeloid leukemia relapsed after allogeneic hematopoietic stem cell transplantation. *European Journal of Haematology*. 2016;96:629–636.
40. Metzelder S, Wang Y, Wollmer E, et al. Compassionate use of sorafenib in FLT3-ITD-positive acute myeloid leukemia: sustained regression before and after allogeneic stem cell transplantation. *Blood*. 2009;113:6567–6571.
41. Legrand F, Floch A-CL, Granata A, et al. Prophylactic donor lymphocyte infusion after allogeneic stem cell transplantation for high-risk AML. *Bone marrow transplantation*. 2016;52:620–621.
42. Cauchois R, Castagna L, Pagliardini T, et al. Prophylactic donor lymphocyte infusions after haploidentical haematopoietic stem cell transplantation for high risk haematological malignancies: a retrospective bicentric analysis of serial infusions of increasing doses of CD3+ cells. *Br J Haematol*. 2018;85:570–573.