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The results of conventional allogeneic stem cell transplantation (SCT) in refractory hematologic malignancies are poor. Sequential strategies have shown promising results in refractory acute myelogenous leukemia (AML), but have not been validated in a haploidentical (Haplo) transplant setting. We have developed a new sequential approach combining chemotherapy with broad antitumor activity (thiotepa 10 mg/kg, etoposide 400 mg/m^2, and cyclophosphamide 1600 mg/m^2 from day -15 to day -10), followed after 3 days of rest by a reduced-intensity conditioning regimen (fludarabine 150 mg/m^2, i.v. busulfan 6.4 mg/kg, and thymoglobulin 5 mg/kg from day -6 to day -2). High-dose post-transplantation cyclophosphamide was added in cases with Haplo donors. Seventy-two patients (median age, 54 years) with a refractory hematologic malignancy (44 with acute myelogenous leukemia, 7 with acute lymphoblastic leukemia, 15 with myelodysplastic syndrome/myeloproliferative neoplasms, and 6 with lymphomas) were included in this retrospective multicenter study. Donors were Haplo (n = 27), matched related (MRD; n = 16), and unrelated (UD; n = 29). With a median follow-up of 21 months, the 2-year overall survival (OS) and event-free survival (EFS) were 54.7% and 49.3%, respectively, in recipients of Haplo transplants, 49.2% and 43.8%, respectively, in recipients of MRD transplants, and 37.9% and 28%, respectively, in recipients of UD transplants. Compared with UD, the outcomes were improved in Haplo in terms of the incidences of acute grade II-IV graft-versus-host disease (GVHD) (11.1% versus 41.4%; $P < .001$) and GVHD-free, relapse-free survival (44.4 versus 10.3%; $P = .022$). These results support the safety and efficacy of a thiotepa-based sequential approach in allogeneic SCT with a Haplo donor with post-transplantation immune modulation. Thus, in patients with refractory hematologic malignancies, there seems to be no benefit in searching for a UD when a Haplo donor is readily available.

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INTRODUCTION

Despite recent therapeutic advances, the prognosis for patients with relapsed or refractory (R/R) hematologic malignancies remains very poor. Only 10% to 20% of patients in primary refractory acute myelogenous leukemia (AML) can achieve a complete response (CR) with another course of chemotherapy. In these patients, the 1-year overall survival (OS) is <20%, with a median duration of <6 months [1-3]. OS ranges from 2 to 8 months after salvage therapy in R/R acute lymphoblastic leukemia (ALL) [4,5], 3 to 10.5 months in lymphoma relapsing after autologous transplantation [6], and <1.5 years in high-risk or blast-phase myeloproliferative neoplasms [7].

Considering these poor results, allogeneic stem cell transplantation (allo-SCT) is the sole therapeutic option with a significant chance of a cure in patients with R/R hematologic malignancies. However, the feasibility of standard myeloablative conditioning (MAC) allo-SCT is limited by both a relatively high incidence of relapse and, especially, high nonrelapse mortality (NRM), which can reach 40% in patients with refractory AML [7-10]. Reduced-intensity conditioning (RIC) allowed for a significant reduction of NRM, expanding the transplantation option to those patients who are ineligible for MAC. Nonetheless, it did not appear to provide sufficient disease control to allow the graft-versus-tumor (GVT) effect in R/R diseases [8-10]. Thus, sequential regimens, adding a short course of intensive of chemotherapy to decrease the malignant cell burden before RIC, have been developed [11,12]. Among the most promising approaches, the sequential FLAMSA (fludarabine, cytarabine, and amsacrine, followed by 4 Gy of total body irradiation [TBI], cyclophosphamide, and antithymocyte globulin [ATG]) strategy has been associated with improved survival in patients with R/R AML, with a 2-year OS of ~40%, compared with 20% to 30% after standard MAC allo-SCT [8,10]. However, the results are still unsatisfactory in terms of severe toxicity (related mainly to amsacrine and TBI) and long-term disease control.

The widespread use of haploidentical family donors allows the rapid identification of an available donor for the majority of patients. T cell-replete haploidentical (Haplo) allo-SCT has now become feasible with the use of post-transplantation cyclophosphamide (PT-CY) [13-15]; however, the sequential regimen has not been validated in a Haplo setting. Only 1 published report on 16 patients with lymphoma seems to support the feasibility of this approach in Haplo [16]. Thus, these results need to be confirmed in a larger number of patients with R/R hematologic malignancies.

For a wider application of such a sequential approach, improvement can be made possible through the use of readily available donors, such as Haplo donors, and conditioning with broad-spectrum chemotherapeutic agents, which might not have been used in previous treatment lines. Among potential agents, thiotepa's ability to prevent central nervous system relapse by crossing the blood-brain barrier and its well-established safety record made it an appealing option for R/R patients [17,18]. Consequently, we have developed a new sequential approach combining induction chemotherapy with thiotepa, etoposide, and cyclophosphamide (TEC) followed by an RIC regimen for the treatment of wide- spectrum refractory hematologic malignancies.

In an attempt to assess the efficacy of this strategy in Haplo, we conducted a multicenter retrospective analysis in patients with R/R hematologic disorders treated with our TEC-RIC regimen, and compared the results in allo-SCT recipients with Haplo donors and those with matched related donors (MRDs) and unrelated donors (UDs).

PATIENTS AND METHODS

Patient Selection

All consecutive patients with an R/R hematologic malignancy who underwent allo-SCT with TEC-RIC sequential conditioning between April 2013 and February 2016 in our 5 centers were included in this study. Participants had to fulfill at least 1 of the following criteria defining refractory disease [19-21]:

- For AML and ALL: (1) primary induction failure (PIF) after 2 or more cycles of chemotherapy, (2) early relapse after a first remission duration of <6 months, (3) relapse refractory to salvage combination chemotherapy containing high-dose cytarabine, (4) primary refractory to 1 cycle of induction chemotherapy and positive minimal residual disease after a second cycle, and (5) primary refractory to 1 cycle of induction chemotherapy and decision to proceed to transplantation without a second line of high-dose chemotherapy to decrease the cumulative toxicity.
- For myelodysplastic syndrome, myeloproliferative neoplasm, and chronic myelomonocytic leukemia: progressive disease after 1 or more cycles of chemotherapy
- For lymphoma: (1) relapse/progression after 1 or more cycles of chemotherapy following a previous autologous SCT (2) unresponsive to 2 or more cycles of chemotherapy.

All patients who proceeded to transplantation provided written informed consent for the use of their data for clinical research, in accordance with the modified Declaration of Helsinki and the local Ethical Committee. Data were collected from clinical files and laboratory and radiologic test results. The data were meticulously cross-checked using various methods of verification, including matching of several sources of data, onsite verification, and computerized searches for discrepancy errors.

HLA Matching and Donor Selection

Molecular high-resolution typing of HLA-A, -B, -C, -DQ, and -DRB1 alleles was performed for each patient and donor. Donors were Haplo in 27 cases, MRD in 16, and UD in 29. UDs were matched at 10 of 10 loci in 22 cases and at 9 of 10 loci in 7. A patient underwent allo-SCT using a Haplo donor if there was no available MRD or UD, or if a suitable UD was unavailable within the appropriate time frame for the patient's malignancy and clinical circumstances. Haplo transplantation was contraindicated in cases of positive serum samples for donor-specific anti-HLA antibodies (cutoff value of >1000 mean fluorescence intensity) [22]. Peripheral blood stem cells were the preferred stem cell source (bone marrow was accepted at the donor's preference), with no ex vivo T cell depletion.

Conditioning Regimens and Graft-versus-Host Disease Prophylaxis

The TEC-RIC regimen consisted of sequential chemotherapy with total doses of thiotepa 10 mg/kg, etoposide 400 mg/m^2, and cyclophosphamide 1600 mg/m^2 on days -15 to -10, followed, after a 3-day rest, by RIC with fludarabine 150 mg/m^2, i.v. busulfan 6.4 mg/kg, and thymoglobulin 5 mg/kg on days -6 to -2. For patients age >60 years and/or with comorbidities, thiotepa, etoposide, and cyclophosphamide total doses were reduced to 5 mg/kg, 300 mg/m^2, and 1200 mg/m^2, respectively. Graft-versus-host disease (GVHD) prophylaxis consisted of cyclosporine (starting on day -3) and mycophenolate mofetil (starting on day -3 in MRD and UD and on day +6 in Haplo) for all patients. PT-CY was added in cases of Haplo (50 mg/kg on days +3 and +5). Filgrastim was administered in Haplo starting on day +6 and continuing until neutrophil engraftment. Preemptive donor lymphocyte infusion (pDLI) was allowed after withdrawal of immunosuppression, in the absence of GVHD. The detailed treatment schedule for Haplo is shown in Figure 1.

Supportive Care

Antimicrobial prophylaxis consisted of acyclovir and trimethoprim-sulfamethoxazole or atovaquone. All patients were screened weekly by real-time PCR for cytomegalovirus (CMV), Epstein-Barr virus (EBV), and *Toxoplasma gondii* until day +100. PT-CY was administered with hyperhydration and i.v. mesna to prevent hemorrhagic cystitis. Prophylaxis for sinusoidal obstruction syndrome or veno-occlusive disease (SOS/VOD) was performed with orally administered ursodeoxycholic acid and low-dose unfractionated heparin. Patients with risk factors for SOS/VOD (n = 9) received prophylactic defibrotide instead of heparin.

Definition of Endpoints

The primary endpoint was the 2-year OS. The secondary endpoints included engraftment, toxicity, GVHD, relapse, nonrelapse mortality (NRM),

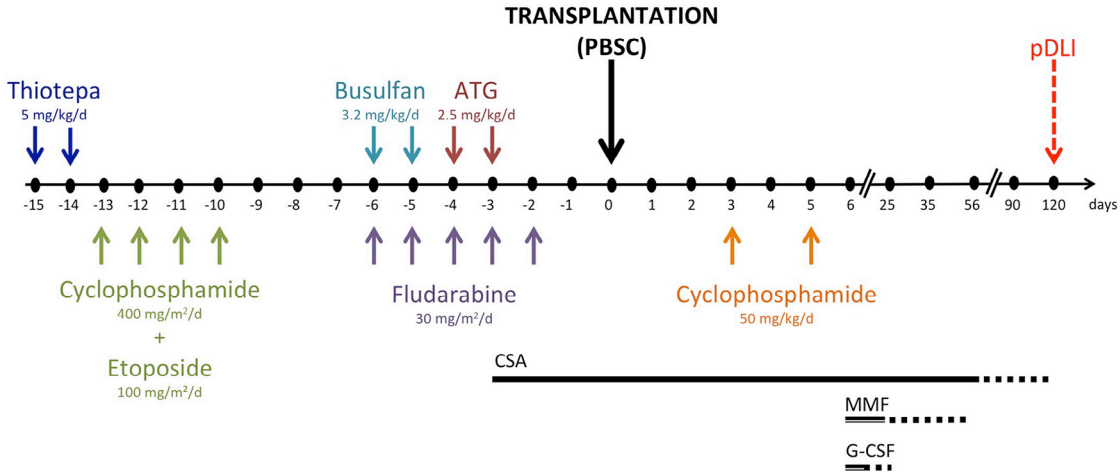

Figure 1. Treatment plan in the haploidentical setting with post-transplantation cyclophosphamide. PBSCs, peripheral blood stem cells; CsA, cysclosporine A; MMF, mycophenolate mofetil.

event-free survival (EFS), and GVHD-free, relapse-free survival (GRFS). OS was defined as the probability of survival (irrespective of the disease state); EFS, as survival with no evidence of relapse; NRM, as death without evidence of relapse; and GRFS, as being alive without grade III-IV acute GVHD, severe chronic GVHD, or disease relapse [23]. Acute and chronic GVHD were diagnosed and graded according to standard criteria [24,25]. Toxicity was evaluated based on the National Cancer Institute's Common Toxicity Criteria scale. Engraftment was defined as an absolute neutrophil count >.5 G/L and a platelet count >20 G/L for 3 consecutive days (the first of which was considered the day of engraftment). Full and mixed donor chimerism were assessed by PCR and defined as the presence of at least 95% and between 6% and 94% leukocytes of donor origin in the peripheral blood, respectively.

Statistical Analysis

Continuous variables were recorded as median and range or as mean ± SD and were compared using the Mann-Whitney *U* test or the *t* test, as appropriate. Qualitative variables were recorded as frequency and percent, and were compared using the chi-square test or Fisher exact test where appropriate. OS, EFS, and GRFS were calculated by the Kaplan-Meier method, and the differences between groups were compared using the log-rank test. Engraftment, GVHD, viral infection, relapse, and NRM were calculated using the cumulative incidence method and analyzed in a time-dependent fashion. For acute and chronic GVHD or relapse, death was considered a competing risk of the event. For NRM, the competing event was relapse. All variables with a significance level of $P < .10$ in the bivariate analyses were introduced into a multivariable Fine and Gray model [26] with backward selection. Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) were computed, with $P < .05$ considered to indicate statistical significance. All analyses were performed with SPSS 20 (IBM, Armonk, NY) and R 3.0 (R Development Core Team, Vienna, Austria).

RESULTS

Patient and Donor Characteristics

Patient and donor characteristics at diagnosis and transplantation are summarized in Tables 1 and 2, respectively. All 72 patients had a refractory hematologic disease, including 44 with AML, 7 with ALL, 8 with myelodysplastic syndrome, 5 with chronic myelomonocytic leukemia, 2 with myeloproliferative neoplasm, and 6 with lymphoma (Table 1). Among the patients with acute leukemia, 34 (30 with AML and 4 with ALL) had persistent excess marrow blasts at the time of transplantation (median, 18%; range, 6% to 95%), 2 patients with AML had persistent leukemic blasts in the peripheral blood, 13 patients (11 with AML and 2 with ALL) had progressive disease at the molecular/cytogenetic level, 1 patient with AML was in second CR after an early relapse (remission duration <6 months), and 1 patient with ALL had persistent hypoplasia. For the entire patient group, the median number of previous treatment lines was 2 (range, 1 to 6), including 7 autologous SCTs and 6 allo-SCTs. There were no significant differences among the Haplo, MRD, and UD groups in terms of sex ratio, Karnofsky Performance Score (KPS), Hematopoietic Cell Transplantation-Specific Comorbidity Index (HCT-CI), donor-recipient sex mismatch, number of previous treatment lines, disease status, and intensity of conditioning. However, Haplo patients were younger than MRD and UD patients ($P = .018$). At the date of analysis, the median duration of follow-up was 21.1 months (range, 8.1 to 43.8 months).

Engraftment and chimerism

Sixty-nine patients engrafted, and 3 died in aplasia (including 1 patient after Haplo). As shown in Table 3, neutrophil and platelet recoveries were moderately delayed in Haplo compared to MRD and UD ($P = .001$ and $P < .001$, respectively). At day +30 after transplantation, full donor chimerism was found in 66 of 69 evaluable patients and in all Haplo patients. Among the 3 patients with mixed chimerism at day +30, 1 patient achieved full donor chimerism at day +90, 1 patient had persistent leukemia and died at day +89, and 1 patient died at day +53 of multiorgan failure.

Acute and chronic GVHD

The cumulative incidences of grade II-IV and grade III-IV acute GVHD were 11.1% and 3.7%, respectively, in Haplo patients (3 grade II and 1 grade III), 12.5% and 0%, respectively, in MRD patients, and 41.4% and 31%, respectively, in UD patients ($P = .031$ and $P = .002$, respectively). There was no significant difference between the Haplo and MRD patients. The cumulative incidence of chronic GVHD was 30% in Haplo patients (including 2 with severe GVHD), 37.5% in MRD patients (1 with severe GVHD), and 31% in UD patients (6 with severe GVHD) ($P = .528$) (Table 3). In multivariate analysis, increased risk of grade II-IV acute GVHD was significantly associated with UD compared to Haplo (HR, 9.47; 95% CI, 2.62 to 34.24; $P = .0006$).

Infection and toxicity

In the Haplo setting, bacterial septicemia was encountered in 13 of 27 patients (48%) and led to sepsis or

Table 1
Disease Status at Transplantation

Disease	Total (n = 72), n (%)	Haplo (n = 27), n (%)	MRD (n = 16), n (%)	UD (n = 29), n (%)
AML	44 (61)	17 (63)	9 (56)	18 (62)
Intermediate karyotype	20 (45)	7 (41)	5 (56)	8 (44)
Unfavorable karyotype	24 (55)	10 (59)	4 (44)	10 (56)
Primary induction failure	10 (14)	4 (15)	4 (25)	2 (7)
Primary refractory to one induction	13 (18)	3 (11)	3 (19)	7 (24)
Positive minimal residual disease after second cycle of induction	4 (6)	0 (0)	2 (13)	2 (7)
Refractory to second line with hypomethylating agent	6 (8)	2 (7)	0 (0)	4 (14)
Untreated	3 (4)	1 (4)	1 (6)	1 (3)
Relapse after first CR <6 mo	10 (14)	3 (11)	2 (13)	5 (17)
Refractory to second line	4 (6)	2 (7)	1 (6)	1 (3)
Untreated	5 (7)	0 (0)	1 (6)	4 (14)
CR2	1 (1)	1 (4)	0 (0)	0 (0)
R/R after CR >6 mo	11 (15)	7 (26)	0 (0)	4 (14)
ALL	7 (10)	3 (11)	2 (13)	2 (7)
Primary induction failure	1 (1)	1 (4)	0 (0)	0 (0)
Relapse after CR1 <6 mo	4 (6)	1 (4)	2 (13)	1 (3)
Refractory to second line	3 (4)	0 (0)	2 (13)	1 (3)
Untreated	1 (1)	1 (4)	0 (0)	0 (0)
R/R after CR >6 mo	2 (3)	1 (4)	0 (0)	1 (3)
Refractory	1 (1)	0 (0)	0 (0)	1 (3)
Hypoplasia with positive minimal residual disease	1 (1)	1 (4)	0 (0)	0 (0)
MDS/MPN	10 (14)	3 (11)	2 (13)	5 (17)
Marrow blasts < 20%	6 (8)	2 (7)	2 (13)	2 (7)
Marrow blasts ≥ 20%	4 (6)	1 (4)	0 (0)	3 (10)
CMML	5 (7)	1 (4)	2 (13)	2 (7)
Marrow blasts <20%	4 (6)	1 (4)	1 (6)	2 (7)
Marrow blasts ≥20%	1 (1)	0 (0)	1 (6)	0 (0)
Lymphoma	6 (8)	3 (11)	1 (6)	2 (7)
Diffuse large B cell lymphoma	3 (4)	1 (4)	0 (0)	2 (7)
Hodgkin's lymphoma	1 (1)	1 (4)	0 (0)	0 (0)
T-cell lymphoma	2 (3)	1 (4)	1 (6)	0 (0)
Progressive disease	2 (3)	0	1 (6)	1 (3)
PR	3 (4)	2 (7)	0 (0)	1 (3)
CR >3	1 (1)	1 (4)	0 (0)	0 (0)

MDS indicates myelodysplastic syndrome; MPN, myeloproliferative neoplasm; CMML, chronic myelomonocytic leukemia; PR, partial response.

Table 2
Patient and Donor Characteristics at Transplantation

Characteristic	Total (n = 72)	Haplo (n = 27)	MRD (n = 16)	UD (n = 29)	*P* Value*
Recipient age, median (range)	54 (16.5-72)	42 (20-72)	55 (29-68)	63 (16.5-70)	.018
Patient sex, female/male, n (%)	41/31 (57/43)	14/13 (52/48)	8/8 (50/50)	19/10 (66/34)	.48
Donor sex, female/male, n (%)	48/24 (67/33)	18/9 (67/33)	6/10 (38/62)	24/5 (83/17)	.009
Sex mismatch†, n (%)	18 (25)	6 (22)	6 (38)	6 (21)	.421
KPS, n (%)					.071
≥90%	33 (46)	17 (63)	5 (31)	11 (38)	
<90%	39 (54)	10 (37)	11 (69)	18 (62)	
HCT-CI, n (%)					.589
0-1	29 (40)	12 (48)	7 (44)	10 (34)	
2-5	43 (60)	13 (52)	9 (56)	19 (66)	
CMV-positive serology, n (%)					
Recipient	42 (58)	18 (67)	11 (69)	13 (45)	.16
Donor	34 (47)	15 (56)	13 (81)	6 (21)	<.001
Previous transplantation, n (%)					.519
Allogeneic SCT	6 (8)	4 (15)	1 (6)	1 (3)	
Autologous SCT	7 (10)	2 (7)	1 (6)	4 (14)	
Stem cell source, n (%)					.017
Bone marrow	7 (10)	6 (22)	1 (6)	0 (0)	
Peripheral blood stem cells	65 (90)	21 (78)	15 (94)	29 (100)	
Conditioning intensity, n (%)					.721
Full	58 (81)	21 (78)	14 (88)	23 (79)	
Reduced	14 (19)	6 (22)	2 (12)	6 (21)	
GVHD prophylaxis, n (%)					
CsA and MMF	69 (96)	27 (100)	14 (88)	28 (97)	.136
ATG	69 (96)	24 (89)	16 (100)	29 (100)	.074

* Comparison of the Haplo, MRD, and UD groups using the Mann-Whitney *U* test or the chi-square test, as appropriate.
† Sex mismatch is defined as male recipient who received a graft from a female donor.

Table 3
Transplantation-Related Events

Event	Total (n = 72)	Haplo (n = 27)	MRD (n = 16)	UD (n = 29)	*P* Value*
Follow-up, mo, median (range)	21.1 (8.1-43.8)	16.4 (8.1-43.8)	24.8 (12.5-36.1)	22.1 (11-43.5)	
Neutrophil engraftment, n (%)	69 (96)	26 (96)	15 (94)	28 (97)	.893
Day of ANC >.5 G/L, median (range)	15 (10-47)	18.5 (13-32)	13 (10-17)	14 (10-47)	.001
Platelet engraftment, n (%)	66 (92)	24 (89)	15 (94)	27 (93)	.802
Day of platelet >20 G/L, median (range)	12.5 (0-102)	25.5 (0-102)	11 (8-28)	11 (7-43)	<.0001
Acute GVHD, % cumulative incidence (95% CI)					
Grade II-IV	23.6 (14.5-34)	11.1 (2.7-26.2)	12.5 (1.9-33.6)	41.4 (23.2-58.7)	.027
Grade III-IV	13.9 (7.1-22.9)	3.7 (.3-16.2)	0	31 (15.2-43.8)	.003
Chronic GVHD at 2 yr, % cumulative incidence (95% CI)	32.1 (21.5-43.1)	30 (13.8-48.1)	37.5 (14-61.3)	31 (15-48.6)	.909
Response to treatment at day +30, n (%)					.911
No response	3 (4)	1 (4)	1 (6)	1 (3)	
Complete remission	66 (96)	24 (96)	15 (94)	27 (96)	
Not evaluable	3	2	0	1	
Relapse, % cumulative incidence (95% CI)					
At 1 year	30.7 (20.4-41.6)	30.4 (14-48.6)	31.2 (10.7-54.6)	31 (15.2-48.4)	
At 2 years	38.4 (26.5-50.2)	35.9 (17.2-55)	31.2 (10.7-54.6)	43.1 (23.8-61.1)	.858
NRM, % cumulative incidence (95% CI)					
At 100 days	16.7 (9.1-26.2)	11.1 (2.7-26.2)	12.5 (1.9-33.7)	24.1 (10.4-40.9)	.375
At 1 year	23.7 (14.6-34.1)	14.8 (4.5-30.8)	25 (7.1-48.3)	31 (15.2-48.3)	
At 2 years	23.7 (14.6-34.1)	14.8 (4.5-30.8)	25 (7.1-48.3)	31 (15.2-48.3)	.376
GRFS, % (95% CI)					
At 1 year	46.8 (35.2-58.4)	44.4 (25.7-63.2)	43.8 (19.4-68.1)	20.7 (5.9-35.4)	
At 2 years	28.7 (17.6-39.7)	44.4 (25.7-63.2)	43.8 (19.4-68.1)	10.3 (0-21.4)	.032
EFS, % (95% CI)					
At 1 year	46.8 (35.2-58.4)	54.8 (35.8-73.9)	43.8 (19.4-68.1)	41.1 (23.1-59.1)	
At 2 years	38.9 (26.9-51)	49.3 (29.4-69.3)	43.8 (19.4-68.1)	28 (10.6-45.4)	.320
OS, % (95% CI)					
At 1 year	56.6 (45.1-68.2)	65.8 (47.6-84.1)	56.2 (31.9-80.6)	48.3 (30.1-66.5)	
At 2 years	46.4 (33.7-59)	54.7 (34-75.4)	49.2 (24.3-74.1)	37.9 (18.5-57.4)	.381

ANC indicates absolute neutrophil count.
* Comparison of the Haplo, MRD, and MUD groups.

septic shock in 5 patients. Four patients required transfer to an intensive care unit, among whom 2 died, 1 at day +8 and the other at day +26. Six patients were successfully treated for fungal infection. CMV and EBV reactivations were observed in 13 (48%) and 17 (63%) patients, respectively. Hemorrhagic cystitis with BK virus occurred in 8 patients (29.6%), including 6 requiring irrigation. Among nonhematologic adverse events unrelated to GVHD or infection, 3 grade 3 events occurred in 3 patients, and SOS/VOD occurred in 2 patients. Mucositis was observed in 74% of Haplo patients, with a maximum grade of 3 in 1 patient. Adverse events in MRD and UD patients did not differ significantly from those in Haplo patients, as shown in Table 4.

Disease response and outcomes

At day +30, 69 patients were evaluable for response and 3 had died. Sixty-six patients (95.7%) were in CR and 3 had persistent active disease (1 Haplo, 1 MRD, and 1 UD) (Table 3). Relapse occurred in 28 patients, at a median of 136 days after allo-SCT (range, 26 to 827 days). At the time of this report, 6 patients were still alive, at 36 to 525 days after relapse. The 2-year cumulative incidence of relapse was 35.9% in Haplo patients, 31.2% in MRD patients, and 43.1% in UD patients ($P = .86$).

Of the 72 patients included in this study, 39 died and 33 were still alive at the last follow-up. Death was directly attributed to disease progression or relapse in 21 patients and related to allo-SCT in 18 patients (11 due to infection and 7 due to GVHD). The 2-year NRM, OS, EFS, and GRFS were 23.7%, 46.4%, 38.9%, and 28.7%, respectively, for the entire patient cohort and 14.8%, 54.7%, 49.3%, and 44.4%, respectively, for the Haplo patient group ($P = .38$, .38, .32, and .032, respectively) (Table 3 and Figure 2). In the 44 patients with AML, the 2-year NRM, OS, EFS, and GRFS were 15.9%, 41.5%, 37.5%, and 21.9%, respectively.

In univariate analysis, there was no significant difference in terms of outcomes according to patient age, sex, HCT-CI, CMV donor/recipient serology status, history of previous transplantation, type of hematologic disease, or thiotepa dose. In multivariate analysis, the incidence of relapse, NRM, OS, and EFS were not significantly influenced by the type of donor

Table 4
Nonhematologic Organ Toxicity According to World Health Organization Criteria

Toxicity	Total (n = 72)		Haplo (n = 27)		MRD (n = 16)		UD (n = 29)	
	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4
Mucositis	7	1	1	0	2	0	4	1
Gut	8	2	2	0	1	0	5	2
Liver	3	2	2	1	0	0	1	1
Acute kidney injury	2	2	2	2	0	0	0	0
Heart failure	1	1	0	0	1	0	0	1
Lung	0	2	0	0	0	1	0	1

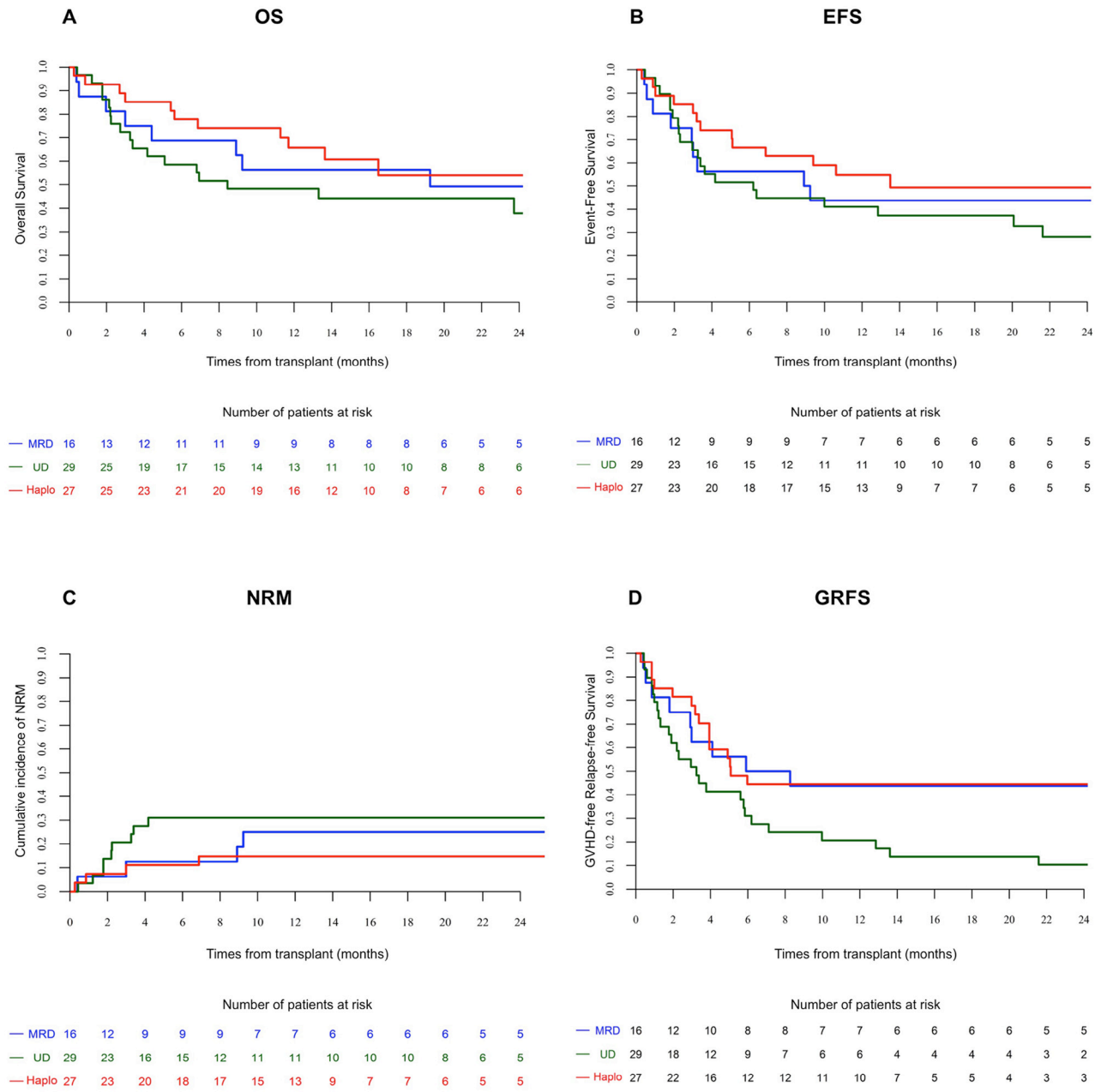

Figure 2. Estimated 2-year OS (A), EFS (B), cumulative incidence of NRM (C), and GRFS (D) according to the type of donor.

(Haplo versus MRD versus UD), patient age, or KPS. UD transplantation had a detrimental impact on GRFS compared with Haplo transplantation (HR, 2.26; 95% CI, 1.13 to 14.52; $P = .022$) (Table 5).

pDLI

Only 13 patients (18%; 9 with AML, 2 with ALL, and 2 with lymphoma) received pDLI, with a first infusion between day +71 and day +244. The median number of transfusions was

Table 5
Multivariate Analysis

Variable	NRM			GRFS			EFS			OS		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value	HR	95% CI	*P* Value	HR	95% CI	*P* Value
MRD	1			1			1			1		
UD versu MRD	1.23	.38-4.03	.730	1.86	.90-3.83	.09	1.02	.49-2.14	.954	1.29	.58-2.89	.529
Haplo versus MRD	.60	.15-2.49	.485	.83	.37-1.86	.64	.7	.30-1.61	.403	.84	.34-2.09	.710
Patient age	.998	.96-1.04	.920	.99	.97-1.01	.374	1.003	.98-1.03	.813	1.001	.98-1.03	.958
KPS <90%	3.1	.98-9.82	.054	1.35	.77-2.39	.297	1.68	.90-3.14	.105	1.53	.79-2.96	.207

All patient and transplantation characteristics, including conditioning regimens, were assessed for inclusion into the multivariate analyses. All variables with a significance level of $P < .10$ in the bivariate analyses were introduced into a multivariate model.

2 (range, 1 to 4). Five additional patients received DLI because of disease relapse (3 with AML, 1 with lymphoma) or loss of chimerism (1 patient). In the Haplo group, 6 of 27 patients received pDLI (starting dose of 1×10^5 $CD3^+$ cells/kg or 1×10^6 $CD3^+$ cells/kg). Chronic GVHD developed in 6 patients after pDLI (including 3 Haplo patients), including 4 severe forms, and was reversible in 5 patients.

To enhance the GVT effect, 3 patients received azacytidine and 1 patient received targeted therapy with the FLT3-specific tyrosine kinase inhibitor (TKI) sorafenib in combination with pDLI. None of these patients relapsed, and the toxicity was easily managed. Of note, azacytidine and/or sorafenib were given to 3 additional patients in whom DLI was contraindicated. At last follow-up, 9 of 13 patients were alive after pDLI; 8 were in CR, 4 had relapsed, and 1 had died of GVHD.

DISCUSSION

Findings from this study suggest that sequential conditioning is feasible in a Haplo setting with PT-CY and induces limited toxicity while retaining broad antitumor activity. Compared with UD, the outcomes were improved in Haplo in terms of incidence of acute GVHD and GRFS. Although the Haplo patients were younger than the UD patients on average, recipient age did not influence the outcomes in multivariable analysis. There was no significant difference in terms of toxicity and outcomes between Haplo and MRD patients. Thus, for these advanced patients, one should look first for a related donor, either matched or Haplo. Searching for a UD may delay the procedure, with a risk of losing the opportunity for transplantation, and may be associated with worse outcomes compared with Haplo.

In our heavily pretreated refractory population, with a median age of 54 years, KPS <90% in 54% of patients and an HCT-CI ≥2 in 60% of patients, we observed a 2-year NRM rate of 14.8% in the Haplo patients. This is in line with the reported NRM rates in Haplo with RIC or MAC in retrospective studies, including patients with a low to very high Disease Risk Index [13,15,27-33]. The 1-year NRM was 15% in the original study reported by Luznik et al. [13] and 17% in a recent large retrospective study of 116 patients [33]. Our results compare favorably with MAC Haplo in patients with active disease at transplantation, for whom Raiola et al. [28] reported a 6-month NRM of 26%, versus 9% for patients in remission. Thus, adding a short intensive course of thiotepa-based chemotherapy before RIC did not seem to increase the toxicity in a Haplo setting with PT-CY.

In the whole patient cohort, the 2-year NRM rate was 23.7%. This compares favorably with MAC allo-SCT, which is associated with an NRM of ~40% [34,35], and with the sequential FLAMSA strategy, which is associated with an NRM of 22.2% to 33% [11,12,36,37]. It is also consistent with a retrospective study that reported a 1-year NRM of 24% after allo-SCT for AML in PIF, with no significant difference among FLAMSA, MAC, and RIC [38]. More recently, results of a prospective trial with a clofarabine-based sequential regimen (combination of clofarabine and cytarabine, followed by cyclophosphamide, busulfan, and ATG) showed a significant improvement in terms of toxicity, with a low NRM of 12% at 2 years. However, relapse remained the main complication in these patients with PIF, and the 2-year EFS was 29% [21]. In comparison, the 2-year EFS in our study was 46.2% in AML patients with PIF, and 37.5% in all patients with AML.

Our approach, substituting amsacrine, cytarabine, and TBI with thiotepa, cyclophosphamide, etoposide, and i.v. busulfan, seemed to fulfill the objective of exerting a broad-spectrum antitumor activity. In patients with various R/R hematologic malignancies, the CR rate was 95.7% by day +30 post-transplantation. In patients with AML, including 55% (24 of 44) with unfavorable cytogenetics (including 12 with a monosomal karyotype) and 41% (18 of 44) with secondary AML, the CR rate was 95.2%. This is higher than the 88% CR achieved by day +30 using the FLAMSA approach and the 45% CR achieved with RIC allo-SCT [12,39].

The 2-year OS was 54.7% in Haplo, which is superior to the 40% reported with the FLAMSA regimen, the 38% reported with clofarabine-based sequential conditioning, and the 20% to 30% reported after MAC allo-SCT [11,21,35,40]. For the whole patient cohort and the patients with AML, the OS was similar to that with FLAMSA and clofarabine-based regimens. Our study population may appear heterogeneous, but the type of malignancy and disease status at transplantation did not significantly influence the final outcomes. Although longer follow-up is needed, our results are especially encouraging for patients with monosomal karyotype, with a 1-year OS of 57.1% and a 1-year EFS of 40%.

To our knowledge this is the first reported study using ATG in a Haplo setting with PT-CY. We aimed to reduce the risk of GVHD without increasing the incidence of relapse, as has been shown in conventional allo-SCT [41-43]. The incidence of acute grade II-IV GVHD was 11.1%, and that of severe chronic GVHD was 10%. These results seem to compare favorably with those of other studies, which have reported cumulative incidences of 14% to 31% of acute grade II-IV GHVD and of 0 to 38% of severe chronic GHVD without ATG [13,14,27-33,44]. Despite the use of ATG in patients with progressive disease, the 2-year relapse incidence was 35.9% in Haplo patients. This is comparable to the reported relapse incidences of 33% in patients with active disease who received MAC Haplo without ATG and 37% in those who the FLAMSA regimen [11,28]. Overall, ATG in Haplo with sequential conditioning was associated with low rates of GVHD without compromising outcomes in R/R patients.

Early administration of the hypomethylating agent azacytidine in patients with AML has been reported to be well tolerated and to result in a low incidence of GVHD [45]. This approach in association with pDLI could enhance the graft-versus-leukemia effect and is also being evaluated in a prospective trial (NCT 01541280) in high-risk AML patients. Preliminary data and a recent report case report suggest that FLT3 TKIs also could be effective for patients with FLT3 internal tandem duplication in the post-transplantation setting [46-48]. Because of the retrospective nature of this study, immunomodulation combining pDLI with early administration of preventive azacytidine or sorafenib was not proposed for all patients. Our promising results in the 13 selected patients who received this treatment show that it is feasible in Haplo after sequential conditioning and suggest that it should be administered to all high-risk patients in the absence of GVHD.

In conclusion, our TEC-RIC sequential conditioning regimen seems to be a safe and valid platform in a Haplo setting with PT-CY for patients with refractory hematologic diseases. Compared with MRD allo-SCT, toxicities and GVHD were not increased, and survival was not inferior in Haplo. Interestingly, the Haplo group had a lower incidence of acute GVHD and a higher GRFS compared with the UD group. Thus, this study does not support the use of an UD when a Haplo donor is readily available, especially in refractory hematologic malignancies when time is of the essence. The TEC-RIC regimen

allows for a high rate of post-transplantation CR and thus can be proposed for any type of refractory hematologic malignancy. Two prospective multicenter studies (NCT 03079089 and NCT 03035422) based on this new sequential approach, including early post-transplantation immuno-intervention, are currently being scheduled.

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Authorship statement: M.M. designed the study, supervised research, analyzed data, and wrote the manuscript. R.D. designed the study; collected, assembled, and analyzed data; performed statistical analysis; and wrote the manuscript. A.L.M., S.C., J.E.C., S.F., J.D., and M.T.R. collected, assembled and analyzed data; recruited patients; and helped write the manuscript. M.L. analyzed data, performed statistical analysis, and commented on the manuscript. F.G., A.R., E.B., G.B., F.M., R.B., S.S., A.V., F.D., O.R., and O.L. recruited patients and helped write the manuscript. All authors approved submission of the manuscript for publication purposes.

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