Biol Blood Marrow Transplant 20 (2014) 1573–1579

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Unmanipulated Haploidentical Transplants Compared with Other Alternative Donors and Matched Sibling Grafts

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Article history:
Received 28 April 2014
Accepted 30 May 2014

Key Words:
Unrelated
Haploidentical
Cord blood
Allogeneic transplant

A B S T R A C T

We studied 459 consecutive patients with hematologic malignancies, median age 44 years (range, 15 to 71 years), who underwent transplantation with grafts from identical sibling donors (SIB; n = 176), matched unrelated donors (MUD; n = 43), mismatched unrelated donors (mmUD; n = 43), unrelated cord blood (UCB; n = 105) or HLA-haploidentical family donors (HAPLO; n = 92). Graft-versus-host disease (GVHD) prophylaxis consisted of cyclosporine and methotrexate in the SIB recipients; antithymocyte globulin for the MUD, mmUD, and UCB recipients; and post-transplantation cyclophosphamide, cyclosporine, and mycophenolate in the HAPLO recipients. Conditioning regimens were mostly myeloablative (69%). Advanced disease phase was more frequent, but not significantly so, in the HAPLO and mmUD groups ($P = .08$). Acute GVHD grade II-IV was significantly less frequent in the HAPLO, UCB, and MUD groups (14% to 21%) compared with the SIB (31%) and mmUD (42%) groups ($P < .001$), and there was a trend toward less moderate-severe chronic GVHD in the HAPLO and UCB groups ($P = .053$). The proportion of patients off cyclosporine at 1 year ranged from 55% for the SIB group to 81% for the HAPLO group ($P < .001$). Transplantation-related mortality at 2 years was lower in the HAPLO and SIB groups (18% to 24%) compared with the MUD, mmUD, and UCB groups (33% to 35%; $P = .10$). Relapse rate was comparable in the 5 groups ($P = .80$). The 4-year actuarial survival was 45% in the SIB group, 43% in the MUD group, 40% in the mmUD group, 34% in the UCB group, and 52% in the HAPLO group ($P = .10$). In multivariate analysis, advanced disease was a negative predictor of survival (hazard ratio [HR], 2.4; $P < .0001$), together with a diagnosis of acute leukemia (HR, 1.8; $P = .0001$); HAPLO grafts were comparable to SIB ($P = .80$), whereas UCB had inferior survival ($P = .03$). In conclusion, unmanipulated haploidentical family donor transplants are an additional option for patients lacking a matched sibling donor.

INTRODUCTION

In the absence of a family matched donor for stem cell transplantation, several alternative stem cell sources are now available, including unrelated volunteer donors (UDs) selected through the International Network of Registries [1], single or double umbilical cord blood (UCB) units [2], or an HLA-mismatched family donor, also referred to as haplo-mismatched (HAPLO) [3]. For the latter, T cell depletion (TCD) programs [4], CD34 selection [3], and, more recently, B cell depletion together with selective TCD [5] have been used to prevent graft-versus-host disease (GVHD) with encouraging outcomes, comparable to those obtained with UCB transplantation [6]. Problems with TCD or CD34-selected HAPLO transplants are associated with the technology and cost involved in graft manipulation and with slow immune recovery, with a high incidence of infectious complications; consequently, transplantation-related mortality (TRM) has remained high [7]. The introduction of unmanipulated HAPLO transplants some years ago has overcome the issues of technology and costs, with encouraging early results [8] that were recently confirmed [9].

In one of these programs, initiated in Baltimore [9], a reduced-intensity conditioning (RIC) regimen, followed by an unmanipulated HAPLO bone marrow transplant,

Financial disclosure: See Acknowledgments on page 1578.
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1083-8791/$ – see front matter © 2014 American Society for Blood and Marrow Transplantation.
http://dx.doi.org/10.1016/j.bbmt.2014.05.029

post-transplantation high-dose cyclophosphamide (PT-CY), tacrolimus, and mycophenolate (MMF), resulted in a high rate of stable engraftment, a low risk of graft versus host disease (GVHD) [9]. We recently reported that a myeloablative conditioning regimen followed by unmanipulated HAPLO transplantation maintained the beneficial low GVHD rate of PT-CY and ensured a low rate of relapse in patients with active disease at the time of transplantation [10]. We also have used the nonmyeloablative program for patients with Hodgkin disease undergoing HAPLO transplantation, and confirmed the results published by the Baltimore group [11,12].

In our collective practice, we have experience with all of the different alternative donor types. In the present study, we compared the outcomes of transplantation from HAPLO donors with those of transplantation from matched UDs (MUD), mismatched UDs (mmUD), single cord blood units (UCB), and HLA-matched sibling donors (SIB) in the years 2006 to 2012.

PATIENTS AND METHODS

Patients

Eligible for this analysis were 459 patients with hematologic malignancies undergoing a first allogeneic transplantation at our center between January 2006 and July 2012. The minimum follow-up for surviving patients is at least 18 months. Clinical characteristics of the study group are summarized in Table 1. The choice of donor was based on the availability of an HLA-matched (8/8) or -mismatched (7/8) unrelated donor; the second choice would have been a 5/6 or 4/6 UCB unit, and the third choice a HAPLO-mismatched family donor. The expected delay to transplantation was taken into account as well; a patient with active leukemia or lymphoma, would not activate a donor search if it was thought that he or she could not wait 30 to 60 days to find a suitable donor or a UCB unit, and a family HAPLO transplantation was performed instead. Consequently, patients receiving HAPLO grafts were more likely to have advanced disease at the time of transplantation (Table 1). Owing to the short interval between determination of eligibility for transplantation and identification of an available HAPLO donor, the proportion of HAPLO grafts has increased significantly in recent years.

The median age of our patient population was 41 years (range 15 to 71 years), with approximately 40% of patients aged >50 years, with the exception of UCB recipients (Table 1). The most common diagnosis was acute leukemia (>40% of all cases; Table 1). The 215 patients with advanced disease, defined as second complete remission (CR2) or greater, included 193 patients with active disease and 22 in third complete remission (CR3).

European Group for Blood and Marrow Transplantation Score

The European Group for Blood and Marrow Transplantation (EBMT) score incorporates disease phase (first complete remission [CR1], CR2, advanced), recipient age (0 to 20, 21 to 40, >40 years), donor-recipient sex mismatch (female/male versus other), interval between diagnosis and transplantation (</≥1 year), and donor type (SIB versus alternative) [13]. The proportion of patients with a high EBMT score (>2) was comparable in the 3 groups of alternative donor transplant recipients (Table 1).

HLA Matching

All SIB grafts were genotypically HLA matched; the 86 UD transplants included 43 UD 8/8 (HLA-A, -B, -C, and -DRB1) matched (MUD) and 43 UD <8/8 matched (mmUD). UCB units were 5/6 HLA-matched (n = 54), 4/6 matched (n = 48), or 3/6 matched (n = 3). The 92 HAPLO grafts were all 3-4 HLA-A, -B, -C, -DRB1 antigen mismatched.

Conditioning Regimens

Chemotherapy-based myeloablative conditioning regimens included thiotepa (THIO), busulfan (BU), fludarabine (FLU), referred to as TBF herein [14,15] or BU-cyclophosphamide (CY). Regimens based on total body irradiation (TBI) included 9.9 to 12 Gy TBI in fractionated doses, with fludarabine (FLU-TBI) or cyclophosphamide (CY-TBI) [10]. Reduced-intensity conditioning (RIC) regimens included FLU-CY-TBI 200 rads [11] and THIO-CY with or without low-dose melphalan [16]. Both myeloablative and RIC regimens for HAPLO transplantations have been described in detail previously [10,13].

Stem Cell Source

The stem cell source was bone marrow in 302 patients, peripheral blood in 52 patients, and UCB in 105 patients (Table 1). All grafts were unmanipulated. The UCB units were all infused intrabone as described previously [17].

GVHD Prophylaxis

Recipients of HLA-identical SIB grafts received cyclosporin A (CyA) + short-course metothrexate (MTX). Recipients of UD grafts received CyA + MTX + antithymocyte globulin (ATG; Thymoglobulin; Sanofi Aventis, France) 3.75 mg/kg on days −3 and −2 pretransplantation. UCB recipients received CyA + MMF and ATG [17]. Recipients of HAPLO grafts were given CyA from day 0, MMF from day +1, and CY 50 mg/kg on days +3 and +5 [10].

Diagnosis and Treatment of GVHD

The clinical diagnosis of acute and chronic GVHD was based on standard criteria, and confirmed by histological analysis of skin and/or rectal biopsy specimens. First-line and second-line therapy for GVHD was provided according to institutional protocols.

Monitoring of Immune Reconstitution

Patients were monitored on day +100 post-transplantation for immune reconstitution, including serum immunoglobulin levels and lymphocyte subpopulations. IgA serum levels and $CD4^+$ cell counts were considered indicative of immune recovery. All surviving patients had serum IgA available. One hundred fifty-seven SIB recipients, 36 MUD recipients, 37 mmUD recipients, 72 UCB recipients, and 76 HAPLO recipients were studied for CD4 recovery on day +100.

Table 1
Clinical Characteristics by Donor Type (n = 459 patients)

Characteristic	SIB	MUD	mmUD	UCB	HAPLO
Number of patients	176	43	43	105	92
Age >50 yr, n (%)	72 (41)	15 (35)	15 (35)	24 (23)	36 (40)*
Age, yr, median (range)	47 (15-69)	42 (19-66)	47 (17-62)	40 (18-64)	45 (17-69)
Advanced phase (>CR2), n (%)	77 (44)	18 (42)	24 (56)	43 (41)	53 (58)*
Diagnosis					
Acute leukemia, n (%)	85 (48)	19 (43)	19 (43)	70 (66)	39 (43)*
Lymphoma, n	16	4	4	10	25
MPD, n	34	9	10	7	14
MDS, n	36	10	9	16	10
Other, n	5	1	1	2	4
EBMT score >2, n (%)	82 (46)	30 (70)	32 (74)	80 (76)	69 (75)*
CMV serostatus −/−, n (%)†	9 (8)	8 (20)	4 (10)	8 (10)	5 (6)*
Myeloablative regimen, n (%)	98 (55)	31 (72)	31 (72)	87 (83)	71 (77)*
Stem cell source, n (%)					
Bone marrow	156 (89)	26 (60)	28 (65)	—	92 (100)*
Peripheral blood	20 (11)	17 (40)	15 (35)	—	—
UCB	—	—	—	105 (100)	—

* $P < .05$.
† CMV evaluable for serostatus evaluation, n = 362.

Supportive Care

Antimicrobial prophylaxis, started during administration of the conditioning regimen, consisted of standard dose acyclovir, levofloxacine 500 mg/day, and fluconazole 400 mg/day until day +75. Cytomegalovirus (CMV) monitoring with pp65 antigenemia was started on day −7 and continued twice-weekly until day +100; preemptive therapy (ganciclovir or foscarnet) was given to patients positive for CMV antigenemia. Weekly Epstein-Barr virus (EBV) monitoring by PCR was started on day +15 and continued weekly until day +100: preemptive therapy with rituximab was given to patients with a viral load >1000 copies/10^5 mononuclear cells. Weekly monitoring of galactomannan was started on day 0 and continued until day +100, and positive patients received mould active antifungal therapy.

Statistical Analysis

The chi-square test and nonparametric unpaired test were used to compare groups according to clinical characteristics; cumulative incidence rates and survival were calculated. In calculating the cumulative incidence of TRM, the competing risk was relapse; when calculating relapse, the competing risk was TRM. Events for disease-free survival (DFS) were relapse of the original disease or death, whichever occurred first. The log-rank test was used to univariately compare survival curves, and the Gray test was used to univariately compare cumulative incidences.

Further multivariate Cox analysis on survival was run with patient and disease variables and transplantation variables, including the 5 donor types and intensity of the conditioning regimen. Variables with a P value <.15 in univariate analysis were considered for the final multivariate model. Similarly, a multivariate Fine and Gray model [18] were used to assess the impact on cumulative incidence. The multivariate model was built following the same rules as for the Cox model. For the Cox model, hazard ratios (HRs) are reported, whereas for the Fine and Gray model, subhazard ratios (SHRs) are shown. Stata version 11 (StataCorp, College Station, TX) and NCSS 7 (NCSS, Kaysville, UT) were used for computation.

RESULTS

Engraftment and Immune Reconstitution

The median time to a neutrophil count of >0.5 × 10^9/L was 18 days in the SIB group, 17 days in the MUD group, 16 days in the mmUD group, 23 days in the UCB group, and 18 days in the HAPLO group (Table 2). Time to engraftment was comparable in the SIB and all alternative donor groups except UCB, which had significantly slower neutrophil engraftment ($P < .001$). Platelet recovery was significantly slower at all time points in the alternative donor groups compared with the SIB group; day +50 platelet counts were 160 × 10^9/L in the SIB group, 100 × 10^9/L in the MUD group, 110 × 10^9/L in the mmUD group, 40 × 10^9/L in the UCB group, and 118 × 10^9/L in the HAPLO group ($P < .01$). Lymphocyte recovery was slower in the alternative donor graft recipients in the first month post-transplantation, and comparable thereafter. The median day +100 absolute circulating $CD4^+$ lymphocyte count was 229/mm^3 in the SIB group, 106/mm^3 in the MUD group, 90/mm^3 in the mmUD group, 63/mm^3 in the UCB group, and 190/mm^3 in the HAPLO group. Compared with SIB recipients, UCB recipients had significantly lower ($P < .01$) CD4 counts until 6 months post-transplantation. UD graft recipients also have lower CD4 counts at almost every time point. HAPLO recipients had lower counts compared with SIB recipients up to day +50, but were comparable thereafter. At 1 year post-transplantation, all 5 groups had comparable CD4 counts. Median day +100 serum IgA levels were lower in all alternative donor groups compared with the SIB group, especially mmUD recipients (Table 2).

Infections

The cumulative incidence of developing CMV antigenemia was 58% in the SIB group, 60% in the MUD group, 60% in the mmUD group, 68% in the UCB group, and 74% in the HAPLO group ($P = .004$). The cumulative incidence of EBV DNAemia >1000 copies × 10^5 cells was 2% in the SIB group, 14% in the MUD group, 12% in the mmUD group, 5% in the UCB group, and 10% in the HAPLO group ($P = .004$). Of the latter group, 6 of 9 patients with EBV DNAemia >1000 copies × 10^5 cells had Hodgkin disease and had relapsed post-transplantation. Patients with EBV-DNAemia >1000 copies × 10^5 cells were treated with rituximab; no patient died of lymphoproliferative disease.

The proportion of patients with bacterial infections during neutropenia was higher in the alternative donor groups, which corresponds to a higher proportion of patients with lethal infections (Table 3). Fungal infections were more frequent in the alternative donor groups compared with the SIB group (Table 2).

Acute GVHD

The cumulative incidence of acute GVHD (aGVHD) grade II-IV was significantly different across the 5 groups of patients ($P < .001$, Fine and Gray): 31% in the SIB group, 21% in the MUD group, 42% in the mmUD group, 19% in the UCB group, and 14% in the HAPLO group (Figure 1A). In particular, a significant difference was identified between the SIB and HAPLO groups ($P < .001$) and between the MUD and mmUD groups ($P = .003$) (Figure 1A). Sex ($P = .80$), age ($P = .02$), intensity of conditioning ($P = .40$), and disease phase ($P = .70$) did not impact acute GVHD grade II-IV. The cumulative incidence of grade III-IV acute GVHD was 7% in the SIB group, 3% in the MUD group, 9% in the mmUD group, 1% in the UCB group, and 4% in the HAPLO group ($P = .10$).

Table 2
Clinical Outcomes by Donor Type

Outcome	SIB	MUD	mmUD	UCB	HAPLO
Number of patients	176	43	43	105	92
Days to engraftment, median (95% CI)	18 (10-26)	17 (12-37)	16 (10-29)	23 (14-42)*	18 (11-32)
Days to acute GVHD, median (95% CI)	22 (5-95)	19 (7-70)	22 (10-97)	24 (8-87)	32 (5-83)*
CD4 count on day +100, median (95% CI)	229 (20-320)	106 (10-180)*	90 (16-190)*	63 (2-108)*	190 (30-302)
IgA serum level on day +100, mg/dL, median (95% CI)	58 (1-410)	30 (8-262)*	17 (3-113)*	30 (1-300)*	
Patients with infection on day+100, %					
Bacterial	23	36	44	39	25%
Fungal	4	14	9	14	11%
CMV antigenemia	58	60	60	68	74%
Patients off cyclosporin by day +365, %	55	60	57	79*	81%*
Follow-up days, median (95% CI)	730 (6-2840)	907 (8-2822)	426 (2-2834)	372 (2-2672)	576 (11-1578)*

Engraftment was defined as the first day with a neutrophil count >0.5 × 10^9/L. Comparisons were made using the Student t test for 2 groups, with SIB as the comparison group in all cases. Bacterial and fungal infections are expressed as the proportion of patients with infection on day +100; both are significant at the $P < .05$ level. CMV antigenemia is expressed as cumulative incidence; the overall P value is < .01 (Fine and Gray method).

* $P < .05$.

Table 3
Primary Causes of Death by Donor Type (n = 459 Patients)

	SIB	MUD	mmUD	UCB	HAPLO
Number of patients	176	43	43	105	92
Alive, n (%)	92 (52)	20 (47)	18 (42)	38 (36)	52 (57)
Rejection, n (%)	0 (0)	1 (2)	3 (7)	0 (0)	1 (1)
Acute GVHD, n (%)	9 (5)	2 (5)	1 (2)	3 (3)	2 (2)
Chronic GVHD, n (%)	4 (2)	2 (5)	2 (5)	3 (3)	1 (1)
Infections, n (%)	7 (4)	6 (14)	5 (12)	18 (17)	10 (11)
Multiorgan failure, n (%)	7 (4)	2 (5)	1 (2)	7 (7)	0 (0)
Interstitial pneumonia. n (%)	4 (2)	0 (0)	3 (7)	2 (2)	1 (1)
Other, n (%)	5 (4)	1 (2)	0 (0)	4 (4)	1 (1)
Relapse, n (%)	48 (26)	9 (21)	10 (23)	30 (29)	24 (26)

Chronic GVHD

The cumulative incidence of moderate-severe chronic GVHD (cGVHD) was 29% for the SIB group, 22% for the MUD group, 19% for the mmUD group, 23% for the UCB group, and 15% for the HAPLO group, with a borderline significant trend ($P = .053$) toward less cGVHD in the UCB and HAPLO groups (Figure 1B).

Discontinuation of Immunosuppressive Therapy

The number of patients with records evaluable on day +180 was 128 in the SIB group, 32 in the MUD group, 30 in the mmUD group, 62 in the UCB group, and 55 in the HAPLO group. The proportion of patients off CYAclosporine on day +180 was 42% in the SIB group, 44% in the MUD group, 42% in the mmUD group, 56% in the UCB group, and 68% in the HAPLO group ($P = .09$). The number of evaluable patients on day +365 was 90 in the SIB group, 28 in the MUD group, 29 in the mmUD group, 47 in the UCB group, and 45 in the HAPLO group, and the responding proportion of patients off CyA in the 5 groups was 55% in the SIB group, 60% in the MUD group, 57% in the mmUD group, 79% in the UCB group, and 81% in the HAPLO group ($P < .001$).

Causes of Death and TRM

Table 3 presents major causes of deaths in the 5 groups. The cumulative incidence of TRM at 1000 days was 24% for the SIB group, 33% for the MUD group, 35% for the mmUD group, 35% for the UCB group, and 18% for the HAPLO group ($P = .10$) (Figure 2). For patients in CR1 or CR2 it was 18% in the SIB group (n = 99), 26% in the MUD group (n = 25), 32% in the mmUD group (n = 19), 37% in the UCB group (n = 62), and 17% in the HAPLO group (n = 39) ($P = .06$). For patients with advanced disease, it was 32% in the SIB group (n = 77), 33% in the MUD group (n = 18), 41% in the mmUD group (n = 24), 33% in the UCB group (n = 43), and 19% in the HAPLO group (n = 53) ($P = .20$). Other variables, including patient age, sex, conditioning regimen, and disease phase, were not predictive of TRM.

Relapse

The cumulative incidence of relapse was 40% in the SIB group, 23% in the MUD group, 30% in the mmUD group, 30% in the UCB group, and 35% in the HAPLO group ($P = .89$) (Figure 3). For patients with early disease (CR1 or CR2), it was 36% in the SIB group, 20% in the MUD group, 15% in the mmUD group, 24% in the UCB group, and 18% in the HAPLO group ($P = .09$). For patients with advanced disease (>CR2), the respective values were 47%, 28%, 42%, 40%, and 47% ($P = .60$). In multivariate analysis, disease phase was associated with a significant increased incidence of relapse (SHR, 2.05; 95% CI, 1.42 to 2.97; $P < .001$). When stratified for myeloablative and RIC regimens, disease phase remained the sole predictor of relapse.

Overall Survival

The actuarial 4-year overall survival was 45% for the SIB group, 43% for the MUD group, 40% for the mmUD group, 34% for the UCB group, and 52% for the HAPLO group ($P = .10$, log-rank test) (Figure 4). When stratified for disease phase, the 4-year actuarial survival in patients in CR1 or CR2 was 53% for the SIB group, 63% for the MUD group, 52% for the mmUD group, 33% for the UCB group, and 57% for the HAPLO

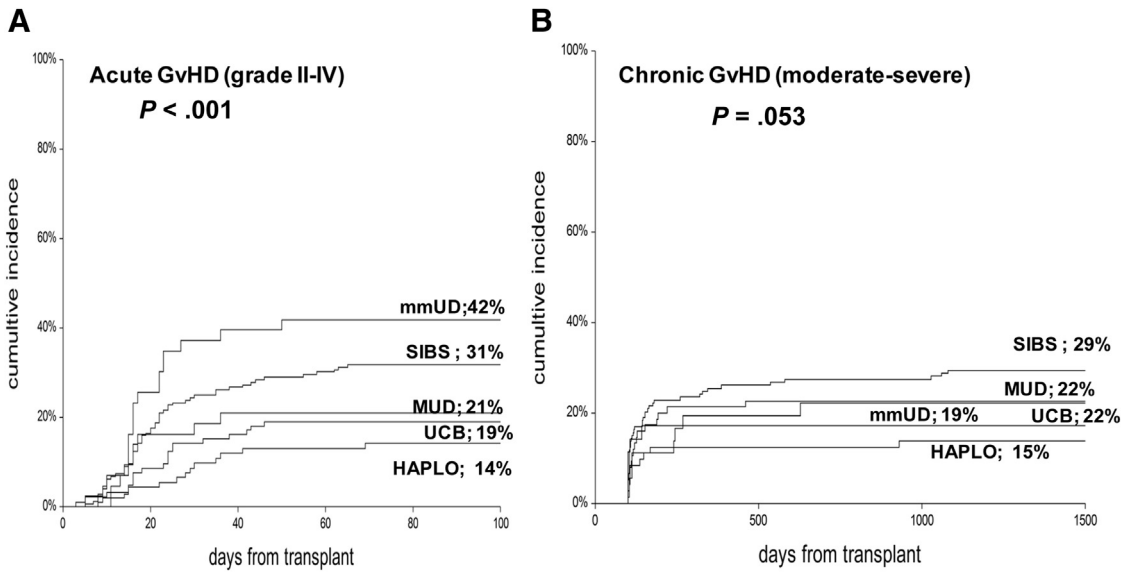

Figure 1. (A) Cumulative incidence of aGVHD. The highest rate for was mismatched unrelated donors (mmUD), followed by siblings (SIB), matched unrelated (MUD), unrelated cord blood (UCB) and haploidentical family donors (HAPLO). The difference is significant ($P < .001$). (B) Cumulative incidence of cGVHD, showing a borderline higher risk for sibling donors.

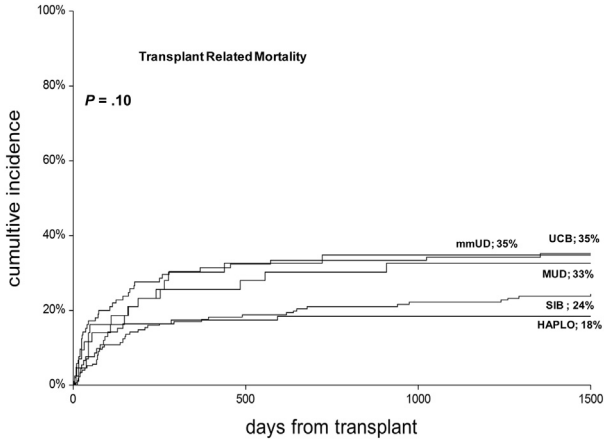

Figure 2. Cumulative incidence of TRM. The UCB, mmUD, and MUD show higher TRM compared with SIB and HAPLO donors; overall the difference is not significant, however.

group ($P = .09$); in patients with advanced disease, respective values were 30%, 31%, 20%, 27%, and 47% ($P = .20$).

DFS

The actuarial 4-year DFS of patients was 32% for the SIB group, 36% for the MUD group, 34% for the mmUD group, 33% for the UCB group, and 43% for the HAPLO group ($P = .20$). When stratified for disease phase, DFS for patients in CR1 or CR2 was 38% for the SIB group, 35% for the MUD group, 40% for the mmUD group, 38% for the UCB group, and 60% for the HAPLO group ($P = .10$); for patients with advanced disease at transplantation, respective values were 22%, 39%, 18%, 28%, and 32% ($P = .60$).

Multivariate Analysis

Variables with a P value $<.15$ were entered into a multivariate Cox model. The most significant negative predictor of survival was disease phase, with an HR of 2.4 for patients with advanced disease versus patients in CR1 or CR2 (Table 4). Other negative predictors were a diagnosis of acute leukemia versus a chronic disorder (HR, 1.8) and the use of UCB graft versus a SIB graft (HR, 1.4); age over the median value of 44 years and female donor/male recipient were not predictive (Table 4). Variables that did not reach the 0.15 level to be entered into the multivariate model were

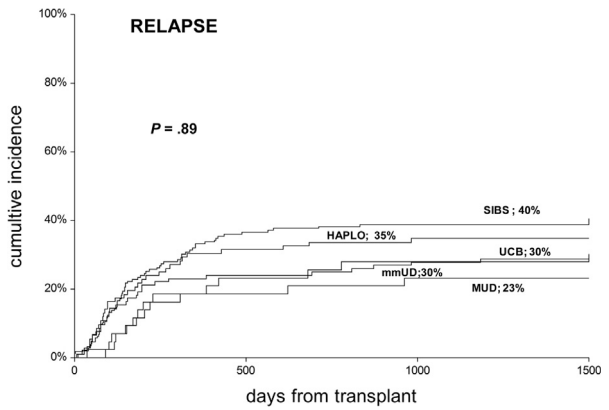

Figure 3. Cumulative incidence of relapse. Slightly higher rates are seen for the SIB and HAPLO groups.

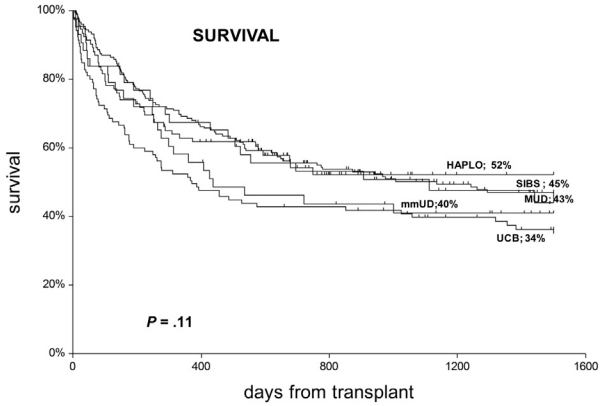

Figure 4. Actuarial survival of patients stratified for donor type. Overall there is no statistically significant difference in survival.

donor sex ($P = .30$), intensity of conditioning regimen (RIC versus myeloablative) ($P = .27$), ABO match ($P = .25$), year of transplantation ($P = .25$), time between diagnosis and transplantation ($P = .95$), and CMV serostatus pre-transplantation ($P = .30$).

DISCUSSION

Unmanipulated haploidentical transplants have become more popular in recent years, supported by encouraging results reported from several different centers [8-12]. This is particularly true in Italy, as demonstrated by the EBMT survey [19], with a rapid increase of HAPLO grafts in the last years, to more than 35 per 10^6 inhabitants, compared with 15 per 10^6 in Germany and <10 per 10^6 in France [19]. Several platforms for unmanipulated HAPLO transplantations are available, including the use of intensive immunosuppression, including ATG, with granulocyte colony-stimulating factor (G-CSF)-mobilized blood and marrow [8], G-CSF–mobilized marrow [15], G-CSF–mobilized peripheral blood [20], or PT-CY with unmanipulated marrow or peripheral blood [11,21]. The latter approach may expose patients to an increased risk of relapse, because cyclophosphamide-induced in vivo depletion of alloreactive T cells may reduce both GVHD and the graft-versus-leukemia effect [9,11,22]. Indeed, in a comparison of PT-CY haploidentical transplants and UCB grafts conditioned with a nonmyeloablative regimen, the relapse rate was higher in the haploidentical transplant recipients, although survival was similar in both groups, owing to a greater risk of TRM in UCB recipients [23].

Table 4
Multivariate Cox Analysis of Survival

Variable	Baseline	Comparison	HR	95% CI	*P* Value
Disease phase	CR1+CR2	Advanced	2.44	1.8-3.2	<.0001
Diagnosis	Chronic disease	Acute leukemia	1.84	1.3-2.5	.0001
Patient age	≤44 yr	>44 yr	1.21	0.9-1.5	.13
Donor type	SIB	MUD	1.01	0.6-1.6	.96
	SIB	mmUD	1.21	0.7-1.8	.40
	SIB	UCB	1.40	1.0-1.9	.03
	SIB	HAPLO	0.95	0.6-1.3	.80
Donor/recipient sex	Other	Female/male	1.14	0.8-1.5	.36

Chronic disease includes lymphoma, myelofibrosis, chronic myelogenous leukemia, myelodysplastic syndrome, and chronic lymphocytic leukemia). Acute leukemia includes acute myelogenous leukemia and acute lymphoblastic leukemia.

The data from the present retrospective study suggest that unmanipulated marrow HAPLO transplants with PT-CY can compare with conventional transplants from other family matched or alternative donors. In a multivariate analysis of survival, HAPLO and MUD grafts yielded overall survival not statistically different from SIB grafts, whereas UCB and mmUD grafts had somewhat inferior outcomes. Advanced disease phase and a diagnosis of acute leukemia were the other 2 negative predictors of survival, in keeping with large registry studies demonstrating the impact of disease and stage risk groups [24].

We were impressed with the relatively low TRM in the HAPLO group both in patients with leukemia receiving myeloablative conditioning and in patients with Hodgkin disease receiving an RIC regimen, confirming our initial experience [10,12]. Compared with SIB recipients, HAPLO recipients had similar TRM, whereas UCB and mmUD recipients had higher TRM. One reason for low TRM is rapid immune recovery; CD4 counts in the HAPLO group were comparable to those in the SIB group and higher than those in the MUD, mmUD, and UCB groups on days +100 and +180. This is not to say that infections were not seen; CMV reactivation in HAPLO grafts was similar to that in the MUD, mmUD, and UCB grafts and greater than that in the SIB grafts. The same can be said for early bacterial infections as well. Mortality due to infection as the primary cause of death was highest in the UCB group (17%) and lowest in the SIB group (4%), whereas the MUD (14%), mmUD (12%), and HAPLO (11%) groups had a similar intermediate risk of lethal infection.

GVHD remains a significant problem in alternative donor transplants, and in this series we could identify 2 groups of patients, one with an average 18% cumulative incidence of developing acute GVHD II-IV and another with an average risk of 36%. The first group included HAPLO, UCB, and MUD recipients, and the second group comprised SIB and mmUD recipients. This distribution was confirmed by multivariate analysis. One may be surprised that SIB grafts carry a high risk of aGVHD, but we still use cyclosporine/methotrexate for SIB grafts, with ATG added for MUD, mmUD, and UCB grafts and PT-CY added for HAPLO grafts. There was also a clear difference between matched and mismatched UD transplants, with significantly more acute GVHD in the mmUD group. The probability of being off cyclosporine at 1 year was significantly higher in the HAPLO group, confirming the low rate of aGVHD and cGVHD, using high-dose post-transplantation cyclophosphamide; however, it should be noted that all HAPLO recipients had unmanipulated bone marrow as the stem cell source. A recent study of PT-CY in patients receiving unmanipulated peripheral blood from haploidentical family donors reported encouraging results in terms of both TRM and survival [21]. Difference between that study and the present study include a greater use of RIC regimens (66% of their patients versus 23% of ours) and a higher rate of extensive cGVHD (38%, compared with 5% of our HAPLO recipients, with bone marrow as the stem cell source). This finding may be relevant for long-term quality of life, showing that unmanipulated peripheral blood with PT-CY following a fully myeloablative conditioning regimen should be used with caution in our opinion.

Relapse remains a significant problem in allogeneic stem cell transplantation [23]. We found a comparable risk of relapse in the 5 different donor groups, with disease phase as the major predictor of relapse in multivariate analysis. This also was true when looking at the effect of donor type separately, in patients who underwent transplantation with early or advanced disease. The comparable risk of relapse in all 5 groups may be related to the fact that we used RIC regimens in only a minority of patients, and, particularly in the HAPLO program, only for those with Hodgkin disease. We therefore confirm our previously reported data [12] suggesting that the combination of a myeloablative conditioning regimen and PT-CY will produce control of the underlying disease, comparable to other conventional transplants. In keeping with this observation, relapse as the primary cause of death did not differ significantly across the 5 groups.

There are several limitations to the present retrospective analysis. First, it was performed in a single center, and our results remain to be confirmed in a multicenter study with varying transplantation policies and procedures and GVHD prophylaxis regimens. Second, it includes both early and advanced patients with both acute and chronic diseases as they entered the unit for an allogeneic transplant. Third, GVHD prophylaxis regimens were different in the 5 groups, though homogeneous for each donor type. ATG was used only in the MUD, mmUD, and UCB groups, whereas PT-CY was used only for in the HAPLO group. The question whether any of these transplant programs may be applicable also to other donor types awaits prospective testing, that is, the same program, including conditioning regimen and GVHD prophylaxis, tested with different donor types. An additional criticism may be that UCB was infused intrabone in this study, in contrast to conventional i.v. infusion: however in a matched-pair analysis, patients receiving a single UCB unit infused intrabone showed a trend toward less relapse and superior DFS compared with patients receiving double UCB units infused i.v. [25].

A strength of the present study is that is reflects real life in a transplantation unit over the last 6 years, with a high proportion of patients with leukemias and myelodysplastic syndromes, including many with advanced disease, often older than 50 or 60 years, the majority searching for alternative donors in the absence of a matched sibling, with little time to maintain a second remission or a suitable clinical condition.

In conclusion, we now have different and competing options for alternative donors for patients who lack an HLA-identical sibling; the outcome appears to be comparable using either MUD or HAPLO grafts, also after correcting for disease phase and diagnosis. Time to identify a suitable donor remains a crucial issue and has, in our recent experience, often shifted the choice to the HAPLO donor. The cost of each procedure, including donor search and stem cell procurement, is an additional issue. A longer follow-up and a larger number of patients will tell us if unmanipulated HAPLO grafts can really compete with grafts from other alternative donors, including MUD, mmUD, or UCB.

ACKNOWLEDGMENTS

Financial disclosure: This work was supported in part by the Associazione Italiana Ricerca Contro il Cancro, Fondazione Ricerca Trapianto Midollo Osseo (FARITMO), Imm Stuarta, and Fondazione Cassa Risparmiop Genova (CARIGE).

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

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