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Matched-Pair Analysis of Transplant from Haploidentical, Unmanipulated Bone Marrow Donor versus HLA Identical Sibling for Patients with Hematologic Malignancies

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A B S T R A C T

A matched-pair analysis of transplant-related outcomes was carried out in 116 of 255 consecutive patients who received transplants from an HLA identical sibling (n = 58) or haploidentical related donor (n = 58). The 2 patient series were matched with 9 variables: period of transplant, patient and donor age, sex, diagnosis, disease phase, conditioning regimen, donor-recipient sex, and cytomegalovirus (CMV) status combinations. As graft-versus-host disease (GVHD) prophylaxis, all patients received the standard cyclosporine and methotrexate association with the addition of anti-thymocyte globulins, mycophenolate mofetil, and basiliximab in haploidentical, unmanipulated bone marrow recipients. Anti-infectious management, transfusion policy, and supportive care were identical for all patients. By comparing the 2 patient series, no statistically significant difference was observed for the cumulative incidence of advanced acute and extensive chronic GVHD, transplant-related mortality, and relapse. With a median follow-up of 3.5 years, the 5-year disease-free survival was 37% ± 6% and 36% ± 6% for HLA identical sibling and haploidentical recipients, respectively. The results of transplant from HLA identical siblings and haploidentical donors are comparable. Regardless of the HLA matching, other factors known to affect the transplant outcomes, such as donor-recipient age, sex, and CMV status combinations, might drive the search for the best donor.

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INTRODUCTION

For many years, the main alternative for patients lacking an HLA-matched family donor has been an 8/8 HLA antigen matched unrelated donor (MUD) allocated through the international registries of volunteer donors [1,2]. However, despite the number of such volunteers exceeding 30 million [3,4], almost two thirds of patients do not proceed to transplantation. The enormous variability of HLA polymorphisms and the time required for identifying a suitable donor are the 2 most important factors limiting the use of MUD transplant, especially for patients at high risk of disease progression who are in urgent need of receiving transplantation. A further alternative graft source is represented by the umbilical cord blood (UCB), which offers a series of advantages such as a faster procurement of cryopreserved hematopoietic stem cells (HSCs), no risk for the donor, low risk of transmissible infections, potentially reduced risk of graft-versus-host disease (GVHD), and less stringent criteria for donor-recipient HLA matching [5,6]. However, the low number of HSCs contained in a single cord blood unit limits its use for transplant, and despite several alternative strategies being currently explored to expand cord blood HSCs [7-11], such limitation remains the main obstacle for successful UCB transplant, particularly in adults.

In more recent years, unmanipulated HSC transplant from haploidentical donors has become a more widespread strategy for patients with high-risk hematologic malignancies lacking an HLA identical sibling. Such a progressive increase of haploidentical transplants results from a series of advantages offered by the procedure: the immediate availability of an haploidentical family donor, the more adjustable management for graft procurement, the absence of problems concerning the HSC dose to be infused, the cost savings for the MUD or UCB search, no requirement of either expensive laboratory facilities or expertise for ex vivo T cell depletion, and, finally, the easier donor availability for post-transplant cellular therapies.

In the absence of randomized trials, several retrospective studies have been produced to compare patients who received transplantation from MUD, UCB, or haploidentical donors as alternative HSC sources for patients lacking an HLA identical sibling. Overall, these studies reported similar probabilities of survival comparing the distinct strategies [12–16,17] so that, in the past years, the selection of an alternative donor has remained a matter of intense debate [18-20]. However, few studies have compared the results between these alternative donors and those provided by the HLA identical sibling [21-26]. Moreover, most of these studies are retrospective and include patients for whom the algorithm and criteria of donor selection were not predefined.

Herein, we report the results of a matched-pair analysis on patients with hematologic malignancies who prospectively underwent transplantation from HLA identical siblings and haploidentical family donors according to the algorithm of donor selection and the uniform transplant policy of the Rome Transplant Network (RTN), a Joint Accreditation Committee ISH-EBMT (JACIE)-accredited metropolitan transplant program established in Rome since 2006.

PATIENTS AND METHODS

Patients

For patients eligible for an allogeneic hematopoietic stem cell transplant, the RTN policy follows an algorithm of donor choice based on a hierarchy according to the following selection criteria: (1) HLA identical sibling; (2) MUD: ≥8/10 HLA antigen matching tested at high resolution for both class I and class II HLA loci; (3) UCB as a single unit selected on the basis of cell dose and number of HLA disparities (0 to 1/6 HLA antigens: TNC ≥2.5 × 10^7/kg and CD34 ≥1 × 10^5/kg; 2/6 HLA: Total Nucleated Cells (TNC) ≥3.5 × 10^7/kg and CD34 ≥2 × 10^5/kg), and (4) granulocyte-colony stimulating factor (G-CSF) primed, unmanipulated bone marrow haploidentical related donor.

Table 1
Patient and Donor Characteristics

Characteristic	Identical Sibling	Haploidentical
Patients		
Number	58	58
Age, median (range), yr	48 (19-64)	42 (15-66)
Sex, n (%)		
Male	33 (57)	32 (55)
Female	25 (43)	26 (45)
Diagnosis, n		
Myeloid	-	-
Acute leukemia	32	32
Myeloid dysplastic syndrome	2	
Secondary leukemia	2	4
Lymphoid		
Acute leukemia	10	9
Non-Hodgkin lymphoma	6	7
Hodgkin lymphoma	4	4
Multiple myeloma	2	2
Disease status, n (%)		
Myeloid		
Early (CR1, CR2)	26 (45)	27 (46)
Advanced	10 (17)	9 (16)
Lymphoid		
Early (CR1, CR2)	8 (14)	8 (14)
Advanced	14 (24)	14 (24)
Conditioning regimen, n (%)		
Myeloablative	41 (71)	39 (67)
Reduced intensity	17 (29)	19 (33)
GVHD prophylaxis	MTX, CSA	ATG, Basiliximab, MTX, CSA, MMF
Donors		
Age, median (range), yr	45 (18-73)	44 (18-70)
Sex match, n (%)		
Female donor/male recipient	14 (24)	14 (24)
Others	44 (76)	44 (76)
CMV match, n (%)		
Negative donor/ positive recipient	7 (12)	7 (12)
Others	51 (88)	51 (88)

MTX indicates methotrexate; CSA, cyclosporine; ATG, anti-thymocyte globulin; MMF, mycophenolate mofetil.

Between January 2008 and December 2012, 255 consecutive patients underwent an allogeneic HSC transplant according to an identical program. In total, 116 of these patients, of whom 58 underwent transplantation from an HLA identical sibling and 58 from an haploidentical family donor, were considered for this matched-pair analysis. The 2 patient series were matched for 9 variables: period of transplant, patient age, patient sex, myeloid or lymphoid malignancy, early (first and second complete remission [CR]) or advanced (third or more CR and active disease) disease status at transplant, myeloablative conditioning (MAC) or reduced-intensity conditioning (RIC) regimen, donor age, donor-recipient sex, and donor-recipient cytomegalovirus (CMV) combination (Table 1). All patients underwent transplantation at the Hematology Stem Cell Transplant Unit of "Tor Vergata" University of Rome.

Conditioning Regimen and GVHD Prophylaxis

Regardless of the HSC source (identical sibling, MUD, UCB, or haploidentical), the RTN policy considers an identical chemotherapy-based conditioning regimen as described by the Spanish group for cord blood transplantation [27]. All patients aged <55 years with a Sorror score ≤2 [28] were prepared with

the TBF-MAC combining thiotepa (5 mg/kg/d i.v. infusion at days −7 and −6), busulfan (3.2 mg/kg/d i.v. infusion over 3 hours at days −5, −4, and −3), and fludarabine (50 mg/m^2/d i.v. infusion over 1 hour at days −5, −4, and −3); patients ≥55 years old or with a Sorror score >2 were conditioned with the RIC version of the Thiotepa Busulphan Fludarabine (TBF) regimen (TBF-RIC) by eliminating 1 dose of thiotepa and busulfan, respectively. As GVHD prophylaxis, all patients received the classic association of methotrexate at days 1 (15 mg/m^2) and 3, 6, and 11 (10 mg/m^2) and cyclosporine. As previously reported [29], for the recipients of an haploidentical transplant, the GVHD prophylaxis was intensified by including the Anti T Lymphocyte Globuline (Grafalon, Neovii Biotech, Germany) at a dose of 5 mg/kg at days −5, −4, −3, −2; mycophenolate mofetil, administered orally at 15 mg/kg/d in 2 daily doses from days 7 to 100; and basiliximab (Simulect; Novartis Pharma AG, Basel, Switzerland), an anti-CD25 monoclonal antibody, administered at a dose of 20 mg at days 0 (2 hours before graft infusion) and 4. Post-transplant cyclophosphamide was not used.

Hematopoietic Stem Cell Source

All 58 haploidentical patients were grafted with unmanipulated bone marrow (BM) harvested from the posterior iliac crests of donors after priming with 4 μg/kg/d G-CSF given as single, subcutaneous injection for 7 days (from −7 through −1 days). Of the 58 patients received transplantation from HLA identical siblings, 20 (15 early and 5 advanced) were grafted with BM and 38 (19 early and 19 advanced) with HSCs collected from peripheral blood (PB) after donor priming with 5 μg/kg/12-hour G-CSF over 3 days.

Infection Management, Transfusion Policy, and Supportive Care

All patients were hospitalized in rooms with high-efficiency particle-arresting filtered air and received an identical anti-infectious prophylaxis with (1) oral trimethoprim-sulfamethoxazole from days −10 to −2 and from hematopoietic recovery until the achievement of CD4$^+$ T cell counts above 200 × 10^6/L, (2) fluconazole from days −10 to +100, (3) acyclovir from day −1 to immunologic recovery, and (4) ciprofloxacin from day −1. Monitoring, diagnosis, and therapy management for bacterial, fungal, and viral infections; transfusion policy and supportive care were identical for all patients. All blood products were irradiated with 2500 cGy.

Definitions

Engraftment was defined as the first of 3 consecutive days with an absolute neutrophil count of ≥0.5 × 10^9/L. Chimerism was evaluated on BM cells or PB cells on days 30, 90, 180, and 365. Sex-mismatched donor-recipient chimerism was evaluated by cytogenetic G-banding or fluorescence in situ hybridization. Sex-matched donor-recipient chimerism was assessed by PCR-based analyses of polymorphic microsatellite regions by short number tandem repeats. HLA typing was performed after transplantation as confirmation of engraftment in haploidentical recipients. The incidence of acute and chronic GVHD was evaluated in all patients with evidence of engraftment and classified by Glucksberg [30] and Seattle criteria [31], respectively. Transplant-related mortality (TRM) was defined as death from any cause except relapse. Relapse was assessed by molecular, cytogenetic, or morphologic evidence of the original hematologic disease in PB, BM, or any extramedullary site. Overall survival (OS) and disease-free survival (DFS) were defined as time to death from all causes and time to relapse or death in remission, respectively.

Statistical Analysis

For matched-pair analysis, sample selection was referred to the transplant period from 2008 to 2012 and carried out with the SAS (SAS Institute, Cary, NC) "survey select" procedure. The final matching was performed for (1) period of transplant (2008 to 2012), (2) patient sex, (3) patient age, (4) diagnosis (lymphoid or myeloid malignancy), (5) disease status at transplant (early or advanced), (6) conditioning regimen (MAC or RIC), (7) donor age, (8) donor-recipient sex, and (9) donor-recipient CMV combinations. An analysis of demographic and clinical characteristics of the patients was performed using descriptive techniques, including mean, median, standard deviation, range, minimum and maximum value for continuous variables, and absolute and relative frequencies for categorical variables. Using parametric and nonparametric statistical procedures (chi-square test and Fisher exact test), the possible interdependence between 2 or more variables was evaluated. For all statistics, a *P*value of <.05 was considered statistically significant. The cumulative incidence (CI) of neutrophil and platelet engraftment, acute and chronic GVHD, TRM, and disease relapse was estimated with competing risk analysis [32], considering relapse or TRM as competing events for engraftment and acute and chronic GVHD. Relapse and TRM were considered reciprocal competing risks. The curves of various subgroups were compared using the Gray test [33]. OS and DFS curves were estimated and plotted by the Kaplan-Meier product-limit method [34], and significant differences were tested using the log-rank test [35]. A 2-tailed value <.05 was considered statistically significant. Due to the small sample size, no multivariate analysis could be conducted because of a lack of model fit. All the analyses were conducted using software SAS 9.3.1 (SAS Institute) and Foundation for Statistical Computing, Vienna, Austria R version 2.15.0.

RESULTS

Engraftment

The CI of neutrophil engraftment was 95% ± 3% with a median of 19 days (range, 12 to 23) and 97% ± 3% with a median of 18 days (range, 10 to 27) in haploidentical and identical sibling patients (*P* = ns), respectively. For all engrafted patients evaluable through the follow-up, the chimerism was of full donor origin.

GVHD

The CI of grade II to IV acute GVHD was 42% ± 7% in haploidentical and 18% ± 5% in identical sibling recipients (*P* = .002). However, the CI of grade III to IV acute GVHD was not statistically different between haploidentical and identical sibling patients: 14% ± 5% versus 7% ± 3% (*P* = ns). The 24-month CI of extensive chronic GVHD was identical between the 2 patient series: 23% ± 7% versus 23% ± 6%.

TRM and Infection-Related Mortality

Although not statistically significant, the CI of TRM at 6 months and 5 years was higher in haploidentical patients than in patients who received transplantation from identical siblings (28% ± 6% versus 14% ± 5%, *P* = .08). No substantial difference of TRM was observed at 5 years (36% ± 6% versus 30% ± 6%, *P* = ns) (Figure 1A). Infections occurred more frequently among haploidentical patients: +12% from sepsis, +12% from central venous catheter (CVC) infections, +20% from urinary tract infections, +4% from sinusitis, +5% from central nervous system infections, +5% from invasive fungal infections, and +9% from ≥3 CMV reactivations. Furthermore, there was a significantly higher incidence of hemorrhagic cystitis occurring in the group of patients who received transplantation from haploidentical donors (31% versus 3.4%, *P*< .001). The CI of infection-related mortality (IRM) was significantly higher in haploidentical patients than in identical sibling recipients at 6 months (26% ± 6% versus 10% ± 4%, *P* = .04). The IRM between the 2 patient series was not statistically different at 5 years (31% ± 6% versus 23% ± 6%, *P* = ns) (Figure 1B).

Disease Relapse

The 5-year CI of relapse was lower for haploidentical recipients than for identical sibling patients (28% ± 6% versus 40% ± 7%, *P* = ns), either receiving transplantation in the early disease phase (20% ± 7% versus 30% ± 7%, *P* = ns) or in the advanced

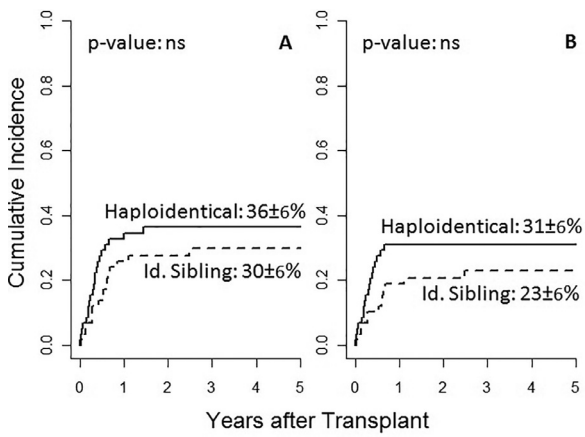

Figure 1. Cumulative incidence of TRM (A) and IRM (B).

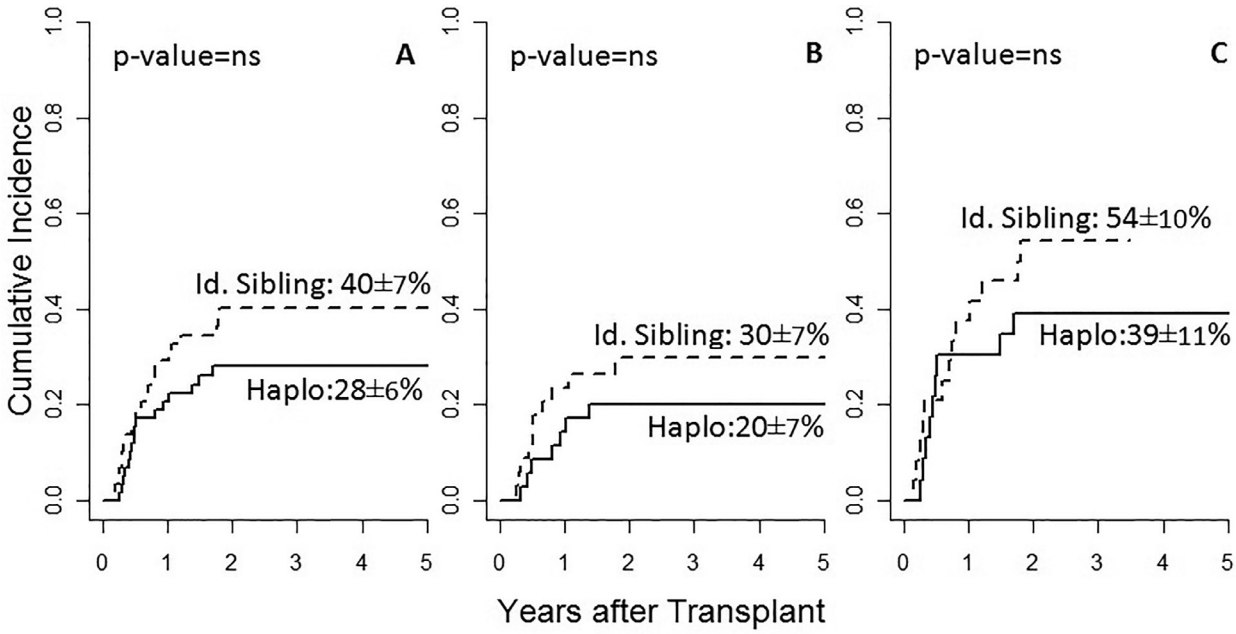

Figure 2. Cumulative incidence of relapse in all patients (A) and patients undergoing transplantation in the early (B) and advanced (C) disease phase.

phase (39% ± 11% versus 54% ± 10%, *P* = ns), but the difference did not reach statistical significance (Figure 2A-C) .

OS

The 1- and 5-year probability of OS for haploidentical and identical sibling recipients was 50% ± 7% versus 63% ± 6% (*P* = ns) and 36% ± 7% versus 49% ± 7% (*P* = ns), respectively. For haploidentical patients who underwent transplantation in the early disease phase, the 5-year survival was similar to that of identical sibling recipients (53% ± 9% versus 57% ± 9%, *P* = ns), while the OS of haploidentical patients transplanted in the advanced disease phase was significantly lower than that of identical sibling recipients (13% ± 7% versus 37% ± 10%, *P* = .049).

DFS

The probability of DFS for haploidentical and identical sibling recipients was 45% ± 7% versus 50% ± 7% (*P* = ns) at 1 year and 36% ± 6% versus 37% ± 6% (*P* = ns) at 5 years, respectively. For haploidentical patients who underwent transplantation in the early or advanced disease phase, the 5-year DFS was similar to that of identical sibling recipients (early: 51% ± 6% versus 53% ± 9%, *P* = ns; advanced: 13% ± 7% versus 17% ± 8%, *P* = ns) (Figure 3A-C).

DISCUSSION

This study shows that on the long-term follow-up, no significant difference is seen in terms of DFS between patients who received transplantation from an HLA identical sibling and those grafted from an haploidentical donor. Our observations are made through a matched-pair analysis of consecutive patients who prospectively underwent transplantation at a single center according to a unique JACIE-accredited transplant program that followed an identical transplant policy for patient selection, donor search, conditioning regimen, and

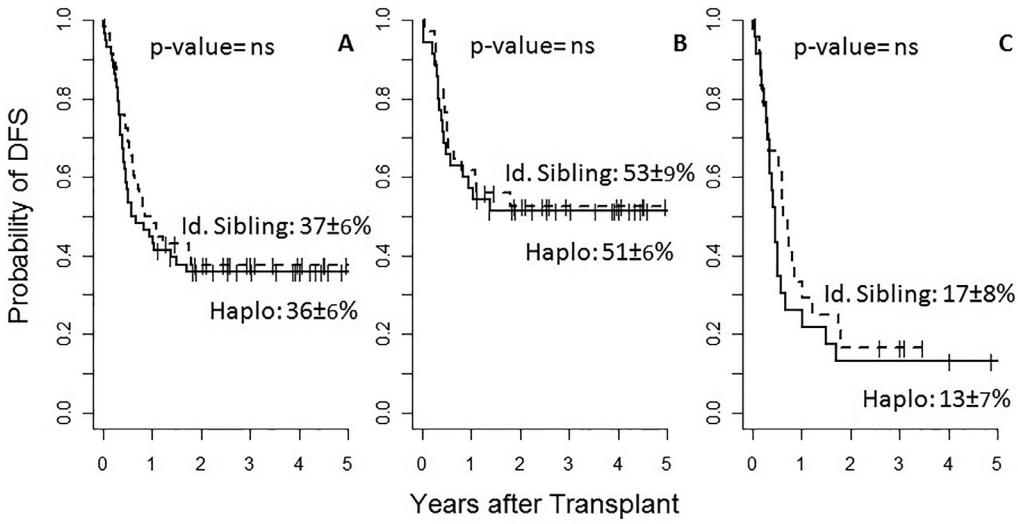

Figure 3. Probability of DFS of all patients (A) and patients undergoing transplantation in the early (B) and advanced (C) disease phase.

GVHD prevention. Furthermore, monitoring, diagnosis, prophylaxis and therapy of infectious diseases, transfusion therapy, and supportive care were identical for all patients. Together with the high number of variables for which the 2 patient series were matched, these characteristics of our study contribute to strengthen the value of the reported results.

The equivalent long-term outcome observed in the 2 series could be due to the counterbalance between a significantly higher IRM occurring early after transplant among haploidentical patients and the higher (although not statistically significant) incidence of relapse observed in identical sibling recipients. HLA disparity, higher intensity of GVHD prophylaxis, increased incidence of grade ≥2 acute GVHD, and, consequently, the more immunosuppressive therapy given for its control are all factors contributing to expose haploidentical patients to a higher risk of infections. On the other hand, both HLA disparity and higher incidence of acute GVHD in haploidentical patients might account for the reduced risk of relapse through a more pronounced graft-versus-leukemia effect in these patients compared with identical sibling recipients.

Several comparative studies have reported similar outcomes for patients who received transplantation from MUD, cord blood, or haploidentical donors [12–16], but few of these studies include patients who received transplantation from HLA identical siblings. No significant difference in terms of the main post-transplant outcomes was reported in a Chinese study comparing patients who received transplantation from haploidentical donor or identical siblings [21]. In this analysis, the median patient age was only 37 years (range, 5 to 50), and 16% of patients in the cohort of haploidentical patients were mismatched for just 1 HLA antigen. Furthermore, haploidentical patients were significantly younger than patients in the identical sibling group. Finally, the 2 patient series were unbalanced for several other factors such as disease distribution, stem cell source, and graft composition. In a retrospective study reported by Bashey et al. [22], the adjusted DFS and OS at 2 years were similar between the 3 patient groups consisting of 117 identical siblings, 101 MUDs, and 53 haploidentical recipients affected by hematologic malignancies. However, the distribution of conditioning regimens and graft composition were significantly unbalanced and the follow-up was short. Although very heterogeneous for patient characteristics and transplant procedures, the study from Raiola et al. [23] did not find any significant difference of survival at 4 years between identical sibling (n = 176), MUD (n = 43), mismatched unrelated donor (MMUD) (n = 43), cord blood (n = 105), and haploidentical (n = 92) transplants. In a series of 227 patients (87 identical sibling, 108 MUD, 32 haploidentical) quite uniform in terms of diagnosis (acute myelogenous leukemia/myelodysplastic syndrome (MDS)) and conditioning regimen, Di Stasi et al. [24] reported a similar 3-year progression-free survival. The major limits of this study consist of the low number of patients in remission and the characteristics of haploidentical patients who were significantly younger and presented a lower comorbidity index than the identical sibling and MUD recipients. Taken together, all the above studies agree in recognizing an equivalent final outcome for identical sibling and haploidentical transplants. However, their relevance is limited by the heterogeneity of the patient series and the retrospective nature of the analysis. Finally, the Chinese group reported the results of 2 prospective, multicenter trials conducted, respectively, on 450 adult patients with acute myelogenous leukemia who had intermediate- or high-risk disease in first CR, comparing 231 haploidentical recipients with 219 patients who received transplantation from identical siblings [25], and on 210 adult patients with Ph-negative, high-risk acute lymphoblastic leukemia in first CR, of whom 186 ultimately underwent transplantation, 83 from identical siblings and 103 from haploidentical donors [26]. In both studies, the 3-year DFS was similar between identical sibling and haploidentical recipients. Although from the European Blood and Marrow Transplantation Group (EBMT) retrospective study, no significant difference between identical sibling and haploidentical patients was observed in the cumulative incidence of relapse [36], our results are in line with the observation of the Chinese group, which reports a superior graft-versus-leukemia effect associated with haploidentical transplantation compared with HLA-identical sibling donor graft for high-risk acute leukemia [37]. HSC transplant from HLA identical siblings remains the reference model in evaluating outcomes of patients undergoing transplantation from other alternative HSC sources. Considering all the advantages related to the use of a haploidentical family donor for patients lacking an HLA identical sibling, this matched-pair analysis was deliberately restricted to the familiar setting with exclusion of MUD recipients and UCB patients, whose number was, furthermore, too low for matching. Although the number of patients sets some limits to its statistical relevance, our analysis based on data produced prospectively by a predefined global strategy and a uniform transplant policy further supports the equivalence of haploidentical patients with respect to identical sibling recipients regarding the long-term outcome. As a final conclusion, we can speculate that, in perspective, HLA matching is unlikely to remain the first criterion for donor identification, yet other factors known to affect the transplant outcomes such as features of donor-recipient combinations could drive the search for the best donor.

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Authorship statement: W.A., R.C., and A.P designed the study, analyzed the data, and wrote the manuscript; R.C., L.C., A.P., G.D.A., B.M., P.D.F., T.D., L.C., A.M., F.M., M.C.T., O.A., A.T., A. F., and M.C. selected and treated patients, contributed data, and critically reviewed the manuscript; L.S. and M.A. provided laboratory data and guidance in infectious complications; M.A. and C.R. provided HLA typing and chimerism study; I.M., A.B., B.A., and A.P. managed data and coordinated the search for the alternative donor; G.A. provided transfusional and supportive care; S.M. coordinated the data center. All authors read and approved the final version of the manuscript.

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