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Allelic HLA Matching and Pair Origin Are Favorable Prognostic Factors for Unrelated Hematopoietic Stem Cell Transplantation in Neoplastic Hematologic Diseases: An Italian Analysis by the Gruppo Italiano Trapianto di Cellule Staminali e Terapie Cellulari, Italian Bone Marrow Donor Registry, and Associazione Italiana di Immunogenetica e Biologia dei Trapianti

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mm indicates mismatch.
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HLA molecules are important for immunoreactivity in allogeneic hematopoietic stem cell transplantation (HSCT). The Gruppo Italiano Trapianto di Cellule Staminali e Terapie Cellulari, Italian Bone Marrow Donor Registry, and Associazione Italiana di Immunogenetica e Biologia dei Trapianti promoted a retrospective observational study to evaluate HLA matching and the impact of allelic HLA mismatching and non-HLA factors on unrelated Italian HSCT outcomes. From 2012 to 2015, 1788 patients were enrolled in the study. The average donor age was 29 years and the average recipient age was 49 years. As a conditioning regimen, 71% of the patients received myeloablative conditioning. For GVHD prophylaxis, 76% received either antithymocyte or anti-T lymphocyte globulin, cyclosporine A, and methotrexate. Peripheral blood was the stem cell source in 80%. The median duration of follow-up was 53 months. Regarding HLA matching, 50% of donor-recipient pairs were 10/10 matched, 38% had 1 mismatch, and 12% had 2 or more mismatches. A total of 302 pairs shared Italian origin. Four-year overall survival (OS), progression-free survival, GVHD-free relapse-free survival, and relapse rates were 49%, 40%, 22%, and 34%, respectively. The 4-year NRM was 27%, and the 100-day cumulative incidence of grade ≥II acute GVHD (aGVHD) was 26%. In multivariate analysis, 9/10 and ≤8/10 HLA allele-matched pairs were associated with worse OS (P = .04 and .007, respectively), NRM (P = .007 and P < .0001, respectively), and grade III-IV aGVHD (P = .0001 and .01, respectively). Moreover, the incidences of grade II-IV aGVHD (P = .001) and chronic GVHD (P = .002) were significantly lower in Italian pairs. In conclusion, 10/10 HLA matching is a favorable prognostic factor for unrelated HSCT outcome in the Italian population. Moreover, the presence of 2 HLA-mismatched loci was associated with a higher NRM (P < .0001) and grade II-IV aGVHD (P = .006) and a poorer OS (P = .001) compared with 1 HLA-mismatched locus in early or intermediate disease phases. Finally, we found that Italian donor and recipient origin is a favorable prognostic factor for GVHD occurrence.

INTRODUCTION

Hematopoietic allogeneic stem cell transplantation (HSCT) is a potentially curative therapy for several hematologic disorders; however, its application depends on the availability of a suitable donor [1-4]. Notably, the likelihood of finding a high-resolution 8/8 HLA-A-, -B-, -C-, or -DRB1-matched donor in the US National Donor Program Registry is approximately 75% for white Europeans but only 46% for white patients of Middle Eastern or North African descent [5]. This probability decreases to 18% and 16%, respectively, in patients of African or black South and Central American origin. In this context, we previously reported [6] that a well-defined donor identification policy implemented by the Rome Transplant Network increased alternative donor identification from 71% to 78% (P= .007) and increased the final transplantation efficiency from 62% to 74% (P< .001) compared with the overall HSCT activity coordinated by the Italian Bone Marrow Donor Registry (IBMDR).

In terms of clinical outcome, the risk of an HLA mismatch was found to be significantly higher in grade II-IV aGVHD (aGVHD), chronic GVHD (cGVHD), nonrelapse mortality (NRM), and overall mortality compared with 8/8 HLA-matched cases [7-9]. However, it is not yet clear which mismatched locus (HLA-A, -B, -C, -DRB1 or -DQB1) is associated with overall mortality [10,11]. In a recent meta-analysis of 13 studies (3446 total cases), mismatches at HLA class I alleles were associated with lower overall survival (OS) [12]. In contrast, no significant difference was observed with HLA-DQ or -DPB1 mismatches, whereas lower (albeit not significantly so) survival was associated with HLA-DRB1 mismatches [12].

In the attempt to improve the outcome of unrelated HSCTs, 2 studies evaluated the permissive and nonpermissive disparity of class I and II HLAs [13,14]. In addition, Kawase et al. [15] reported that HLA-C mismatch combinations play a crucial role in the graft-versus-leukemia/GVHD effect, thereby decreasing the risk of relapse (P< .003). In contrast, disparities at the HLA-C locus (eg, HLA-C*03:03 versus HLA-C*03:04 and HLA-C*07:01 versus HLA-C*07:02) seem to be permissive in terms of HSCT clinical outcome [13,14]. In a meta-analysis of 6967 unrelated HSCTs conducted in Japan, HLA-B*51:01 was found to be associated with aGVHD in recipient-donor pairs due to a strong linkage disequilibrium between HLA-C*14:02 and HLA-B*51:01, as well as to the effect of HLA-B*51:01 itself [16]. Therefore, mismatched HLA-C*14:02 should be considered a nonpermissive HLA-C mismatch in donor selection, because it is a potentially potent risk factor for severe aGVHD and mortality.

More recently, based on the concept that the extensive polymorphism of the HLA-B locus increases the frequency of mismatching, and given its relationship with an increased incidence of GVHD, Petersdorf et al. [17] evaluated the role of HLA-B exon 1 and found that exon 1 of class I HLA genes encodes leader peptides that may be linked to and presented by HLA-E molecules without being a structural part of mature class I HLA molecules. HLA-B leader peptides are dimorphic for their potential to express methionine or threonine at residue 2, a process that stimulates diverse immune-related effects on T cells and natural killer cells. The latter large retrospective study (33,982 patients) concludes that the nonshared HLA-B loci with mismatched leader peptides confers an increased risk of GVHD,

Table 1
Summary of the Impact of the HLA Matching on HSCT Outcomes

Year	Reference	No. of Patients	Main Results
2007	Lee et al. [9]	3857	Increasing single or double HLA-A, -B, -C, and -DRB1 disparity (both antigenic and allelic) was associated with progressively higher mortality or reduced survival. A single HLA-B or -C mismatched locus was better than an -A or -DRB1 mismatch.
2009	Crocchiolo et al. [30]	805	Single HLA-A, -B, -C, -DRB1, or -DQB1 mismatching was associated with poor survival in early status but not in advanced status (75% of patients) of malignant disease at HSCT. No difference in HSCT outcomes between low-resolution and high-resolution single incompatibility.
2011	Woolfrey et al. [11]	1993	Identification of HLA-C antigen and -B allele and antigen mismatches as unfavorable risk factors for outcomes in PBSC HSCT.
2012	Fleischhauer et al. [20]	8539	TCE matching defines permissive and nonpermissive HLA-DPB1 mismatches. Nonpermissive TCE mismatch at HLA-DPB1 increases the risk of overall mortality.
2014	Fernandez-Vina et al. [13]		Identification of HLA-C 03:03/03:04 as permissiveness incompatibilities due to similar outcomes with 8/8 HLA-matched pairs.
2016	Morishima et al. [16]	6967	Identification of HLA-B*51:01 and HLA-C*14:02 in the pairs and in the recipient, respectively, as risk factors for aGVHD and mortality.
2018	Ayuk et al. BMT [25]	3215	Increasing HLA disparity was associated with inferior OS for 9/10 and ≤8/10, respectively, compared with 10/10.
2020	Lorentino et al. [24]	422	HLA-DPB1 TCE4 matching in 10/10 HLA-matched pairs was an independent prognostic factor for OS, GRFS, TRM, and cGVHD.
2020	Petersdorf et al. [17]	33,982	Mortality and GVHD increase with increasing numbers of HLA mismatches. Single HLA-B disparity increases grade III-IV aGVHD. HLA-B mismatch with the leader mismatch and methionine leader shared allotype is associated with higher risk of aGVHD among the HLA- B mismatches.

PBSCs indicates peripheral blood stem cells.

and that the threonine compared with the methionine leader on the shared HLA-B allotypes significantly reduces the occurrence of GVHD in pairs who underwent unrelated HSCT from donors with a single HLA-B locus incompatibility. These results, if validated in future studies, could help clinicians select the most suitable unrelated mismatched donor.

There are 2 models of DPB1 loci, one based on T cell epitopes (TCE model) shared by subgroups of HLA-DPB1 alleles and the other based on allele expression on the cell surface (expression model) [18]. Several clinical reports have identified a survival disadvantage, related mainly to a higher GVHD risk, in nonpermissive HLA-DPB1-mismatched grafts from a 10/10 compatible unrelated donor [19-22]. However, Pidala et al. [23] reported that both permissive and nonpermissive HLA-DPB1 mismatching in 8/8 HLA-matched cases are associated with an increased incidence of grade II-IV aGVHD and a decreased incidence of relapse. More recently, Lorentino et al. [24] identified HLA-DPB1 TCE4 matching as an independent prognostic factor for OS, GVHD and relapse-free survival (GRFS), NRM, cGVHD, and extensive cGVHD in TCE groups and reported significantly better survival in 422 unrelated 10/10 HLA-matched patients with TCE4-permissive incompatibility compared with their nonpermissive counterparts.

The subdivision of DPB1 into TCE groups allows the identification of permissive and nonpermissive DPB1 loci according to their alloreactivity in both a graft-versus-host and a host-versus-graft direction and is a tool with which to identify the best unrelated donor. Currently, in unrelated donor selection, full matching at HLA-A, -B, -C, and -DRB1 is recommended for optimal HSCT survival, with a few exceptions related to the HLA-C and DRB1 loci (eg, HLA-C*03:03 versus HLA-C*03:04 or HLA-DRB1*14:01 versus HLA-DRB1*14:54), and avoids nonpermissive HLA-DPB1 mismatches, particularly TCE-4 DPB1, in HLA-matched pairs [13,14,24].

Regarding non-HLA features, recipient and donor age and the pair's cytomegalovirus (CMV) serostatus, sex matching, and ABO blood group matching have been associated with transplantation outcomes, albeit with some contrasting results [25-29]. In 2009, a retrospective Italian analysis of 805 pairs found no significant differences in OS, DFS, NRM, or GVHD among adult patients with neoplastic diseases who underwent transplantation with a 10/10 or 9/10 HLA-matched donor [30]. However, when patients were stratified according to disease stage at transplantation, a single HLA incompatibility significantly increased the risk of death in patients who underwent HSCT at an early stage but not in patients who did so at an advanced disease stage. The latter study enrolled only 10/10 high-resolution typed pairs who underwent HSCT between 1999 and 2006 and excluded couples without full HLA typing in an attempt to limit confounding results [30]. Since January 2012, all Italian patients have been typed for HLA at the onset of the unrelated donor search process, which is an advantage over nonselected populations. Table 1 summarizes the main results.

Given the foregoing, the Gruppo Italiano Trapianto di Cellule Staminali e Terapie Cellulari (GITMO), IBMDR, and Associazione Italiana di Immunogenetica e Biologia dei Trapianti (AIBT) joined forces to analyze the impacts of allelic HLA matching, the type of HLA disparity, and non-HLA factors on the clinical outcomes of HSCT in unrelated donors in Italy. The patients enrolled constitute the largest Italian nonoverlapping cohort studied to date, and the observation period was longer than that in previous studies.

METHODS

Patients and Transplants

The cohort comprised patients age ≥18 years who underwent unrelated donor HSCT between January 2012 and December 2015 in 39 Italian transplantation programs. Exclusion criteria included unavailability of HLA-typing of A, B, C, DRB1, and DQB1 loci, nonmalignant disease, second allogeneic transplantation, and ex vivo T cell depletion. Patient informed consent for data analysis for research purposes was obtained according to the Declaration of Helsinki. In this collaborative study, the IBMDR and AIBT provided data regarding HLA and donor characteristics, and the GITMO provided (through PROMISE) clinical and patient outcome data, with a specific focus on GVHD prophylaxis. The study was registered at ClinicalTrials.gov (identifier NCT02827149).

HLA typing of donors and patients was performed for A, B, C, DRB1, and DQB1 loci at high resolution by sequence-based typing and sequence-specific

oligonucleotide probe methods. Typing ambiguities involving the most frequent alleles, designated "common" or "well documented" and null alleles, were resolved using the sequence-specific primer technique [31-33].

Italian origin of the pairs was defined based on the donor and recipient ethnicity and birthplace. Moreover, to rule out a possible selection bias due to the gene flow related to population migration, we compared the Italian HLA frequencies of the pairs with those of a previous study in the Italian population [34] and obtained similar results.

Statistical Analysis

The primary aim of this study was to analyze the impact of donor/recipient HLA matching on GRFS, OS, disease-free survival (DFS), engraftment, relapse rate, NRM, and the incidence of GVHD. Neutrophil engraftment was defined as achievement of an absolute neutrophil count >500 cells/mm^3 for 3 consecutive days. Platelet engraftment was defined as achievement of an absolute platelet count >20 cells/mm^3 for 3 consecutive days without transfusion. aGVHD and cGVHD were defined according to the Glucksberg and Seattle criteria, respectively [35,36]. Endpoint was defined as reported previously [37,38].

The probabilities of DFS, OS, and GRFS were estimated with the Kaplan-Meier method [39]. Cumulative incidence was estimated for engraftment, GVHD, NRM, and relapse to accommodate competing risks [40]. Relapse or progression was a competing risk for NRM, and death from any cause was a competing risk for engraftment and relapse. Relapse or progression and death from any cause were competing risks for GVHD. Univariate comparisons of survival curves were made using the log-rank test [41], and Gray's test was used for univariate comparisons of cumulative incidence functions [42]. The effect of HLA disparities was assessed with 2 Cox multivariate models [43]; the first examined the total number of mismatches as a categorical variable (10/10 versus 9/10 versus ≤8/10), and the second examined the match status for each specific HLA locus (mismatched versus matched). The covariates included in both models were patient age, donor and patient sex (female to male versus other), donor and patient CMV serology, disease status (early versus intermediate versus advanced) [44], the Hematopoietic Stem Cell Transplantation Comorbidity Index (HCT-CI) (≥1 versus 0) [45], Karnofsky Performance Status (KPS; <90% versus ≥90%), conditioning intensity (reduced intensity conditioning [RIC] versus myeloablative conditioning [MAC]), stem cell source (peripheral blood versus bone marrow [BM]), antithymocyte globulin (ATG; yes versus no), Italian origin of both donor and recipient and center effect (≥10 versus <10 transplantations each year). The proportional hazard assumption was met for all variables. The type I error rate was fixed at 0.05. Statistical analyses were performed with SPSS version 22 (IBM, Armonk, NY) and R (R Development Core Team, Vienna, Austria).

RESULTS

Overall Population

A total of 1788 adult recipient-donor pairs typed at high resolution for HLA-A, -B, -C, -DRB1, and -DQB1 loci were enrolled in the study. More than one-half (56%) of the patients were affected by acute leukemia. The median patient age was 49 years (range, 18 to 70 years), and the median donor age was 29 years (range, 18 to 57 years). Based on the European Society for Blood and Marrow Transplantation (EBMT) score [44], 47% patients were in an early disease phase, 25% were in an intermediate stage, and 28% were in an advanced stage. In the overall cohort, the median KPS score was 90% (range, 20% to 100%) and the median HCT-CI was 1 (range, 0 to 7). As shown in Table 2, both recipient and donor were Italian in 302 cases, whereas there was a diversity of ethnic origin in the remaining 1487 pairs. The median duration of follow-up was 53 months (range, 1 to 86 months).

Peripheral blood stem cells and BM were the stem cell source in 82% and 18% of transplant procedures, respectively, depending on donor preference and the transplant program policy of each center. The majority of patients (71.5%) received an MAC regimen. Most MAC and RIC regimens (90%) were total body irradiation-free. As GVHD prophylaxis, the majority of patients (76%) received the following combination: ATG, cyclosporine A, and methotrexate. Details of conditioning and GVHD prophylaxis regimens are reported in Supplementary Tables S1 and S2. Allelic HLA compatibility was 10/10 in 50% of cases, 9/10 in 38% of cases, and ≤8/10 in 12% of cases, with a preferred single mismatching selected on locus A, followed by C, B and DQB1, whereas DRB1 incompatibility was avoided (Supplementary Table S3). The cumulative incidence of 30-day polymorphonuclear neutrophil engraftment was 90% (95% confidence interval [CI], 89% to 91%), and that of 90-day platelet engraftment was 79% (95% CI, 77% to 80%). The median time to achieving engraftment was 17 days (range, 4 to 104 days) for polymorphonuclear neutrophils and 19 days (range, 4 to 756 days) for platelets. The probabilities of 4-year OS, 4-year PFS, 4-year GRFS, and 4-year relapse were 49% (95% CI, 47% to 51%), 40% (95% CI, 38% to 42%), 22% (95% CI, 20% to 24%), and 34% (95% CI, 31% to 36%), respectively. The 4-year cumulative incidence of NRM was 27% (95% CI, 24% to 29%), the 100-day cumulative incidence of aGVHD grade ≥II was 26% (95% CI, 24% to 28%), and the 4-year cumulative incidence of cGVHD and extensive cGVHD were 32% (95% CI, 29% to 34%) and 11% (95% CI, 9% to 12%), respectively.

Table 2
Overall Population Characteristics (N = 1788)

Characteristic	Value
Follow-up for survivors, mo, median (range)	38 (1-76)
HSCT year, n (%)	
2012	421 (24)
2013	449 (25)
2014	454 (25)
2015	464 (26)
Patient age, yr, median (range)	49 (18-70)
Diagnosis, n (%)	
AML	714 (40)
ALL	274 (15)
Mixed phenotype leukemia	16 (1)
MDS or MPN	322 (18)
Lymphoma and myeloma	426 (24)
CLL	36 (2)
Secondary origin disease, n (%)	190 (11)
Disease status at HSCT, n (%)	
Early	847 (47)
Intermediate	445 (25)
Advanced	496 (28)
HCT-CI score, median (range)	1 (0-7)
KPS, median (range)	90 (20-100)
Donor age, years, median (range)	29 (18-57)
Female donor/male recipient, n (%)	305 (17)
Italian recipient/Italian donor, n (%)	302 (17)
Host/donor CMV serostatus, n (%)	
Positive/positive	638 (36)
Positive/negative	778 (44)
Negative/positive	139 (8)
Negative/negative	224 (12)
Missing	10 (0.6)
ABO mismatch, n (%)	
No	577 (32)
Minor	377 (21)
Major	526 (30)
Missing	308 (17)
Type of conditioning, n (%)	
MAC	1278 (71)
RIC	510 (29)
Stem cell source, n (%)	
PBSCs	1462 (82)
BM	326 (18)
ATG-based GVHD prophylaxis, n (%)	1612 (90)

Table 3
Multivariate Analysis Exploring the Effect of Overall HLA Matching

Variable	HR (95% CI)	*P* Value
OS		
Disease status		
Intermediate vs early	1.2 (1.1-1.5)	.15
Advanced vs early	2 (1.7-2.3)	<.0001
HCT-CI score Sorror		
≥1 vs 0	1.2 (1.04-1.4)	.01
Patient age		
≥49 yr vs <49 yr	1.4 (1.2-1.6)	<.0001
HLA matching		
9/10 vs 10/10	1.16 (1.004-1.34)	.04
≤8/10 vs 10/10	1.32 (1.08-1.6)	.007
≤8/10 vs 9/10	1.1 (0.9-1.4)	.25
KPS		
<90% vs ≥90%	1.4 (1.2-1.7)	<.0001
PFS		
Disease status		
Intermediate vs early	1.4 (1.2-1.65)	<.0001
Advanced vs early	2 (1.7-2.3)	<.0001
Center		
≥10 HSCTs/yr vs <10 HSCTs/yr	0.8 (0.7-0.9)	.02
Patient age		
≥49 yr vs <49 yr	1.4 (1.2-1.6)	<.0001
KPS		
<90% vs ≥90%	1.4 (1.2-1.6)	<.0001
GRFS		
Disease status		
Intermediate vs early	1.2 (1.1-1.4)	.003
Advanced vs early	1.7 (1.5-2)	<.0001
Patient age		
≥49 yr vs <49 yr	1.3 (1.1-1.4)	<.0001
HLA matching		
9/10 vs 10/10	1.2 (1.05-1.34)	.005
≤8/10 vs 10/10	1.2 (0.98-1.4)	.07
≤8/10 vs 9/10	1 (0.8-1.2)	.99
KPS		
<90% vs ≥90%	1.3 (1.1-1.45)	<.0001
NRM		
Disease status		
Intermediate vs early	1.15 (0.91-1.46)	.24
Advanced vs early	1.75 (1.4-2.2)	<.0001
Center		
≥10 HSCTs/yr vs <10 HSCTs/yr	0.8 (0.6-0.9)	<.0001
Patient age		
≥49 yr vs <49 yr	1.6 (1.3-1.9)	<.0001
HCT-CI score Sorror		
≥1 vs 0	1.4 (1.13-1.7)	.001
HLA matching		
9/10 vs 10/10	1.3 (1.1-1.5)	.007
≤8/10 vs 10/10	1.6 (1.3-2.2)	<.0001
≤8/10 vs 9/10	1.3 (0.9-1.6)	.11
Relapse		
Disease status		
Intermediate vs early	1.7 (1.4-2.1)	<.0001
Advanced vs early	2.2 (1.8-2.6)	<.0001
KPS		
<90% vs ≥90%	1.6 (1.3-1.9)	<.0001
Grade II-IV aGVHD		
HLA matching		
9/10 vs 10/10	1.44 (1.2-1.7)	.0001
≤8/10 vs 10/10	1.4 (1.1-1.8)	.014
≤8/10 vs 9/10	1 (0.7-1.3)	.83
Italian host/Italian donor		
Yes vs No	0.6 (0.5-0.8)	.001
Grade III-IV aGVHD		
HLA matching		
9/10 vs 10/10	1.8 (1.3-2.4)	.0001
≤8/10 vs 10/10	1.8 (1.1-2.7)	.010
≤8/10 vs 9/10	1 (0.6-1.5)	.88
Host/donor CMV serostatus		
Negative/negative vs other	0.56 (0.3-0.97)	.042
cGVHD		
Disease status		
Intermediate vs early	1 (0.8-1.2)	.83
Advanced vs early	1.3 (1.04-1.6)	.017
HCT-CI score Sorror		
≥1 vs 0	1.34 (1.12-1.6)	.001
Stem cell source		
PBSCs vs BM	1.3 (1.04-1.7)	.02
HLA matching		
9/10 vs 10/10	1.3 (1.1-1.6)	.005
≤8/10 vs 10/10	1.14 (.87-1.5)	.35
≤8/10 vs 9/10	0.9 (0.6-1.1)	.31
Italian host/Italian donor		
Yes vs no	0.7 (0.6-0.96)	.02
Extensive cGVHD		
Italian host/Italian donor		
Yes vs no	0.4 (0.3-0.7)	.002
Donor/host sex		
Female to male vs other	1.4 (1.02-2.05)	.03
Center		
≥10 HSCTs/yr vs <10 HSCTs/yr	1.8 (1.2-2)	.03

Covariates: patient age (according to median value), donor/host sex (female to male vs other), donor/host CMV status (negative/negative vs other), disease status (early vs intermediate vs advanced), HCT-CI Sorror (≥1 vs 0), KPS (<90 vs ≥90), conditioning intensity (MAC vs RIC), stem cell source (PBSCs vs BM), ATG (yes vs no), center (≥10 HSCTs/yr vs <10 HSCTs/yr), Italian host/Italian donor (yes vs no), HLA matching on 5 loci (10/10 vs 9/10 vs ≤8/10).

Effect of Allelic HLA Matching on Outcomes

The univariate comparisons of outcomes in relation to allelic HLA matching are reported in Supplementary Table S4. After adjusting for non-HLA-related factors in multivariate analysis, 9/10 HLA matching was associated with significantly worse clinical outcomes than 10/10 HLA-matching in terms of OS (hazard ratio [HR], 1.16; 95% CI, 1.004 to 1.34; P = .04), GRFS (HR, 1.2; 95% CI, 1.05 to 1.34; P = .005), NRM (HR, 1.3, 95% CI, 1.1 to 1.5; P = .007), grade II-IV and grade III-IV aGVHD (HR, 1.44; 95% CI, 1.2 to 1.7; P= .0001 and HR, 1.8; 95% CI, 1.3 to 2.4; P= .0001), and cGVHD (HR, 1.3; 95% CI, 1.1 to 1.6; P= .005). Moreover, as shown in Table 3, in multivariate analysis, ≤8/10 HLA-matched HSCT was associated with worse outcomes than 10/10 HLA-compatible HSCT, whereas there were no significant differences between 9/10 and ≤8/10 allelic incompatibility in terms of clinical outcomes.

Figures 1 and 2 show the OS, NRM, GRFS, and aGVHD results in relation to HLA matching. When analyzing the effect of a single allelic mismatch at each HLA locus versus 10/10

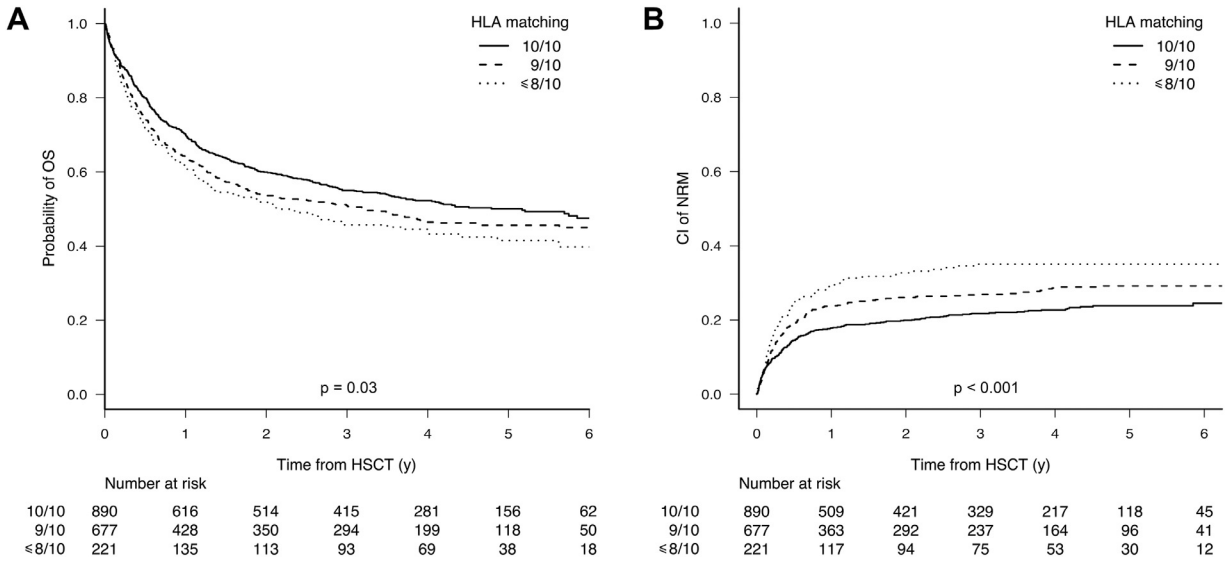

Figure 1. Outcome associations for HLA matching. (A) Kaplan-Meier probabilities for OS and (B) cumulative incidence of NRM stratified for overall HLA matching.

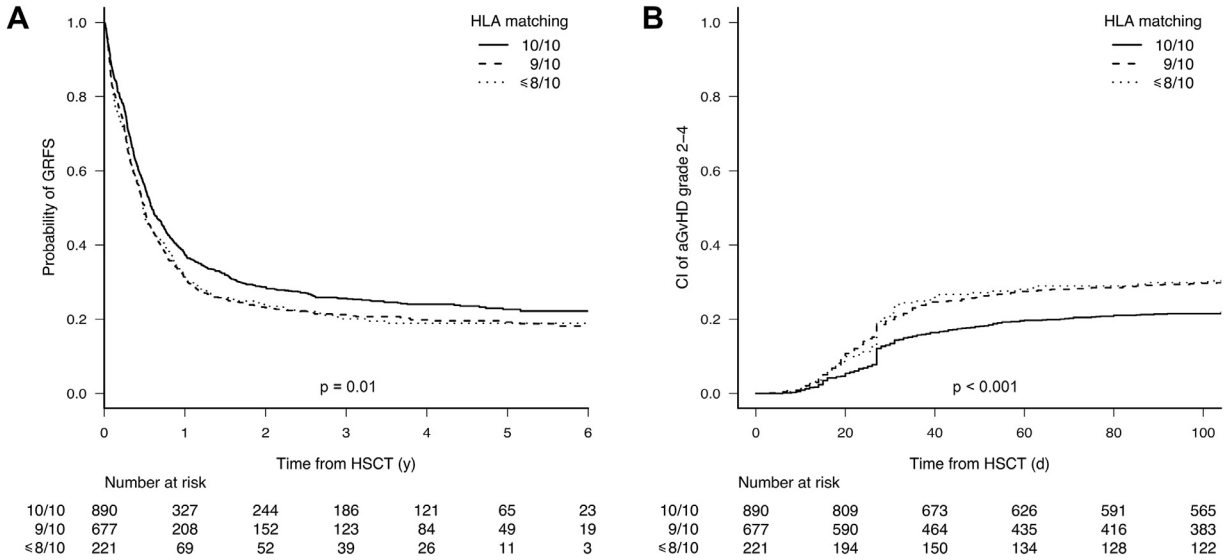

Figure 2. Outcome associations for HLA matching. (A) Kaplan-Meier probabilities for GRFS and (B) cumulative incidence of grade II-IV aGVHD stratified for overall HLA matching.

HLA matching, we found that HLA-B incompatibility was significantly related to a worse outcome in terms of 100-day cumulative incidence of grade II-IV aGVHD (41%; 95% CI, 33% to 49% versus 22%; 95% CI 19% to 24%; P = .0001). It was also worse in terms of the 4-year cumulative incidence of cGVHD (38%; 95% CI, 30% to 46% versus 30%; 95% CI, 27% to 33%; P= .026), relapse incidence (25%; 95% CI, 18% to 33% versus 22%; 95% CI, 19% to 24%; P = .01), NRM (36%; 95% CI, 28% to 44% versus 23%; 95% CI, 20% to 26%; P = .005), and GRFS (16%; 95% CI, 10% to 22% versus 24%; 95% CI, 21% to 27%; P= .0045). In addition, HLA-A-mismatched pairs had a significantly higher 100-day cumulative incidence of grade II-IV aGVHD compared with 10/10 HLA-matched pairs (29%; 95% CI, 24% to 35% versus 22%; 95% CI, 19% to 24%; P= .009), as well as a lower 4-year probability of GRFS (17%; 5% CI, 12% to 22% versus 24%; 95% CI, 21% to 27%; P= .013). In contrast, neither single allelic HLA-C mismatch nor DQB1 mismatch affected transplantation outcomes (Table 4). Multivariate analysis confirmed that HLA-A and HLA-B incompatibility affected clinical outcomes, whereas HLA-C and DQB1 mismatching did not (Table 5).

Impact of HLA Matching on Outcomes According to Disease Status at Transplantation

In patients at an early or intermediate disease phase at transplantation, outcomes were significantly worse in terms of NRM (HR, 1.32; 95% CI, 1.02 to 1.69; P= .032), grade II-IV aGVHD (HR, 1.26; 95% CI, 1.03 to 1.58; P= .047), cGVHD (HR, 1.34; 95% CI, 1.1 to 1.65; P = .005), OS (HR, 1.22; 95% CI, 1.02 to 1.46; P = .03), and GRFS (HR, 1.21; 95% CI, 1.06 to 1.40; P= .005) after a 9/10 HLA-matched HSCT than after a 10/10 HLA-

matched HSCT (Supplementary Table S5). In advanced-phase disease, HLA-mismatching affected only the incidence of aGVHD (Supplementary Table S6).

Subanalysis of Acute Leukemia Patients

We assessed the impact of HLA matching in a subanalysis of 1005 patients affected by acute leukemia. At univariate analysis, donor-recipient HLA matching significantly improved the 100-day cumulative incidence of grade II-IV (P= .02) and grade III-IV aGVHD (P= .035). Moreover, the 4-year probability of GRFS was significantly lower (P= .044) in mismatched pairs (Supplementary Table S7). Multivariate Cox analysis showed that a single-locus HLA mismatch was associated with significantly decreased GRFS and increased grade II-IV aGVHD and cGVHD in all the patients with acute leukemia and in the subset of 815 patients who underwent HSCT at an early or intermediate disease status (Supplementary Tables S8 and S9). In addition, ≤8/10 HLA matching was associated with significantly worse OS (P= .048) and NRM (P= .011) in the early and intermediate phases of acute leukemia compared with 10/10 matched pairs (Supplementary Table S9). Moreover, grade II-IV aGVHD was more frequent in patients with advanced-phase acute leukemia undergoing transplantation from a donor with a 1-locus HLA mismatch compared with those who were fully matched, but without any other relevant consequences (Supplementary Table S10).

Additional Prognostic Factors of Outcomes

The main non-HLA factors associated with OS, PFS, NRM, and GRFS were the patient's age and disease status at transplantation. Moreover, HCT-CI >1 negatively affected OS and NRM, whereas a KPS ≤90% was related to worse results in terms of OS, PFS, and relapse (Table 3). Multivariate Cox analysis, performed according to the patient's disease status at transplantation and acute leukemia subset, produced similar results (Supplementary Tables S5, S6, and S8). Moreover, multivariate analysis of the effect of both overall HLA matching and specific HLA-locus mismatching confirmed the protective role of the BM as the stem cell source in terms of cGVHD.

Given the hypothesis of extended major histocompatibility complex haplotype-matching in individuals of the same ethnic origin [46,47], we investigated whether a shared donor/patient Italian origin could play a protective role in transplantation outcomes. In the 302 pairs in which both donors and recipients were of Italian origin, the risk of grade II-IV aGVHD and cGVHD was significantly lower in the overall cohort of patients (Figure 3). This result was confirmed in terms of grade II-IV aGVHD in the subanalysis of patients who underwent HSCT at an early or intermediate disease phase and in the subgroup of patients with acute leukemia, regardless of the disease status at transplantation (Supplementary Tables S5, S8, S9, and S10). Figure 4 shows the outcomes of grade II-IV aGVHD and GRFS in the Italian pairs at early and intermediate disease phases. As shown in Figure 3B, Italian origin played a meaningful protective role in the occurrence of cGVHD in the overall cohort and in the early and intermediate disease phases (Supplementary Table S5), whereas patients with acute leukemia had a significantly lower incidence of cGVHD only if they underwent HSCT at an early or intermediate disease state (Supplementary Table S9). These overall results confirm that donor origin plays a crucial role in the selection of an unrelated donor, and, consequently, HLA linkage origin should be considered when matching patients and donors. Our analysis also confirms that host/donor CMV-negative serostatus significantly decreases the rate of grade III-IV aGVHD and donor-recipient sex

Table 4
Univariate Analysis of Outcomes According to Single-HLA Locus Mismatch

Variable	100-d Cumulative Incidence of aGVHD Grade ≥II	100-d Cumulative Incidence of aGVHD Grade ≥III	4-yr Cumulative Incidence of cGVHD	4-yr Cumulative Incidence of Extensive cGVHD	4-yr Relapse Incidence	4-yr Cumulative Incidence of NRM	4-yr OS	4-yr PFS	4-yr GRFS
10/10 (n = 890), %	22 (19-24)	7 (6-9)	30 (27-33)	10 (8-12)	36 (32-39)	23 (20-26)	52 (49-56)	42 (39-45)	24 (21-27)
9/10 all mm HLA-A (n = 249), %	29 (24-35)	14 (10-18)	32 (27-38)	13 (9-17)	36 (30-42)	29 (24-35)	46 (39-52)	35 (29-41)	17 (12-22)
P value	.0096	.0009	.47	.235	.77	.06	.211	.136	.013
10/10 (n = 890), %	22 (19-24)	7 (6-9)	30 (27-33)	10 (8-12)	36 (32-39)	23 (20-26)	52 (49-56)	42 (39-45)	24 (21-27)
9/10 all mm HLA-B (n = 141), %	41 (33-49)	17 (11-24)	38 (30-46)	15 (10-22)	25 (18-33)	36 (28-44)	43 (35-52)	39 (31-47)	16 (10-22)
P value	<.0001	.0001	.026	.069	.019	.005	.093	.7	.0045
10/10 (n = 890), %	22 (19-24)	7 (6-9)	30 (27-33)	10 (8-12)	36 (32-39)	23 (20-26)	52 (49-56)	42 (39-45)	24 (21-27)
9/10 all mm HLA-C (n = 173), %	26 (20-33)	10 (6-15)	32 (25-39)	8 (5-13)	38 (30-45)	25 (19-32)	44 (36-51)	37 (30-44)	24 (21-27)
P value	.142	.15	.63	.461	.55	.55	.077	.208	.139
10/10 (n = 890), %	22 (19-24)	7 (6-9)	30 (27-33)	10 (8-12)	36 (32-39)	23 (20-26)	52 (49-56)	42 (39-45)	24 (21-27)
9/10 all mm HLA-DQB (n = 112), %	22 (15-30)	6 (3-12)	34 (26-43)	7 (3-13)	25 (18-34)	24 (17-33)	57 (47-66)	50 (41-59)	29 (21-38)
P value	.684	.954	.34	.33	.05	.57	.67	.243	.634

Table 5
Multivariate Analysis Exploring the Effect of Specific HLA-Locus Mismatch

Variable	HR (95% CI)	*P* Value
OS		
HCT-CI score Sorror		
≥1 vs 0	1.21 (1.04-1.40)	.014
Patient age		
≥49 vs <49	1.37 (1.19-1.60)	<.0001
Disease status		
Intermediate vs early	1.26 (1.05-1.51)	.015
Advanced vs early	2.04 (1.72-2.41)	<.0001
KPS		
≥90% vs <90	0.68 (0.58-0.80)	<.0001
Host/donor CMV serostatus		
Negative/negative vs other combinations	0.76 (0.60-0.96)	.021
PFS		
HCT-CI score Sorror		
≥1 vs 0		
Patient age		
≥49 yr vs <49 yr	1.18 (1.04-1.35)	.013
Disease status		
Intermediate vs early	1.36 (1.15-1.60)	<.0001
Advanced vs early	1.92 (1.64-2.25)	<.0001
KPS		
≥90% vs <90%	0.69 (0.59-0.80)	<.0001
Center		
≥10 HSCTs/yr vs <10 HSCTs/yr	0.83 (0.71-0.96)	.014
HLA-mismatch at locus A		
Mismatch at HLA-A vs 10/10	1.19 (1.002-1.42)	.047
GRFS		
HCT-CI score Sorror		
≥1 vs 0	1.15 (1.02-1.29)	.024
Patient age		
≥49 yr vs <49 yr	1.15 (1.03-1.29)	.018
Disease status		
Intermediate vs early	1.19 (1.03-1.38)	.016
Advanced vs early	1.72 (1.50-1.97)	<.0001
KPS		
≥90% vs <90%	0.78 (0.68-0.90)	<.0001
HLA-mismatch at locus A		
Mismatch at HLA-A vs 10/10	1.25 (1.07-1.46)	.005
HLA-mismatch at locus B		
Mismatch at HLA-B vs 10/10	1.36 (1.12-1.65)	.002
NRM		
HCT-CI score Sorror		
≥1 vs 0	1.39 (1.12-1.72)	.003
Patient age		
≥49 yr vs <49 yr	1.54 (1.25-1.90)	<.0001
Disease status		
Intermediate vs early	1.15 (0.89-1.49)	.299
Advanced vs early	1.81 (1.43-2.29)	<.0001
KPS		
≥90% vs <90%	0.79 (0.62-0.99)	.044
Center		
≥10 HSCTs/yr vs <10 HSCTs/yr	0.78 (0.62-0.99)	.039
HLA-mismatch at locus A		
Mismatch at HLA-A vs 10/10	1.37 (1.05-1.80)	.020
HLA-mismatch at locus B		
Mismatch at HLA-B vs 10/10	1.58 (1.16-2.16)	.004
Relapse		
Disease status		
Intermediate vs early	1.53 (1.24-1.90)	<.0001
Advanced vs early	1.98 (1.61-2.44)	<.0001
KPS		
≥90% vs <90%	0.67 (0.55-0.81)	<.0001
Grade II-IV aGVHD		
Italian host/Italian donor		
Yes vs No	0.65 (0.48-0.86)	.003
HLA-mismatch at locus A		
Mismatch at HLA-A vs 10/10	1.34 (1.04-1.74)	.023
HLA-mismatch at locus B	2.02 (1.53-2.67)	<.0001
Mismatch at HLA-B vs 10/10		
Grade III-IV aGVHD		
HCT-CI score Sorror		
≥1 vs 0	1.62 (1.16-2.27)	.004
HLA-mismatch at locus A		
Mismatch at HLA-A vs 10/10	1.91 (1.30-2.81)	.001
HLA-mismatch at locus B		
Mismatch at HLA-B vs 10/10	2.30 (1.48-3.57)	<.0001
cGVHD		
Donor/host sex		
Female to male vs other combinations	1.34 (1.08-1.67)	.009
HCT-CI score Sorror		
≥1 vs 0	1.38 (1.15-1.66)	.001
Italian host/Italian donor		
Yes vs no	0.70 (0.54-0.91)	.008
Stem cell source		
PBSCs vs BM	1.31 (1.02-1.68)	.036
HLA-mismatch at locus B		
Mismatch at HLA-B Vs 10/10	1.49 (1.12-1.98)	.006
Extensive cGVHD		
Donor/host sex		
Female to male vs other combinations	1.50 (1.04-2.17)	.030
HLA-mismatch at locus B		
Mismatch at HLA-B vs 10/10	1.63 (1.03-2.58)	.038

Covariates: patient age (according to median value), disease status according to EBMT (early vs intermediate vs advanced), donor/host sex (female to male vs other), donor/host CMV status (negative/negative vs other), HCT-CI Sorror (≥1 vs 0), KPS (≥90 vs <90), conditioning intensity (MAC vs RIC), stem cell source (PBSCs vs BM), ATG (yes vs no), center (≥10 HSCTS/yr vs <10 HSCTs/yr), Italian host/Italian donor (yes vs no), mismatch at HLA-A (yes vs no), mismatch at HLA-B (yes vs no), mismatch at HLA-C (yes vs no), and mismatch at HLA-DQB1 (yes vs no).

match (female to male versus other combinations) significantly increases the rate of extensive cGVHD (Table 3).

DISCUSSION

In this study, we evaluated the relationship between donor/recipient HLA matching based on selection criteria for recipients and donors of Italian transplantation programs and the clinical outcomes of the largest Italian cohort of adult neoplastic patients undergoing unrelated HSCT evaluated thus far. We also investigated whether other potential prognostic factors related to the characteristics of pairs might affect HSCT outcome. Crocchiolo et al. [30] investigated HLA mismatches in

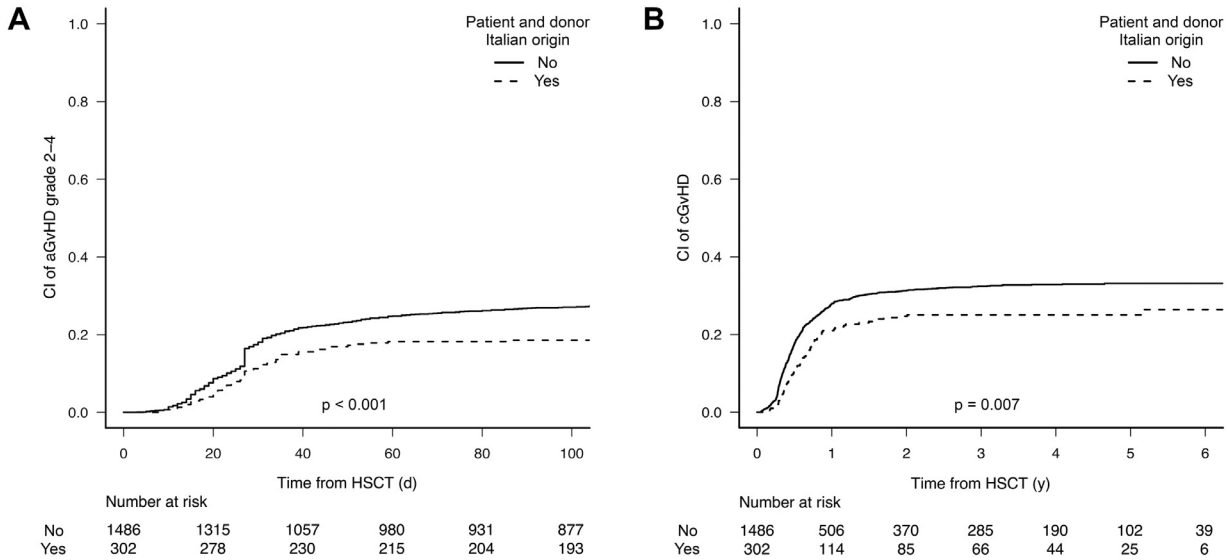

Figure 3. Outcome associations for patient and donor Italian origin in the overall cohort. (A) Cumulative incidence of grade II-IV aGVHD and (B) cumulative incidence of cGVHD stratified for patient and donor Italian origin in the overall cohort.

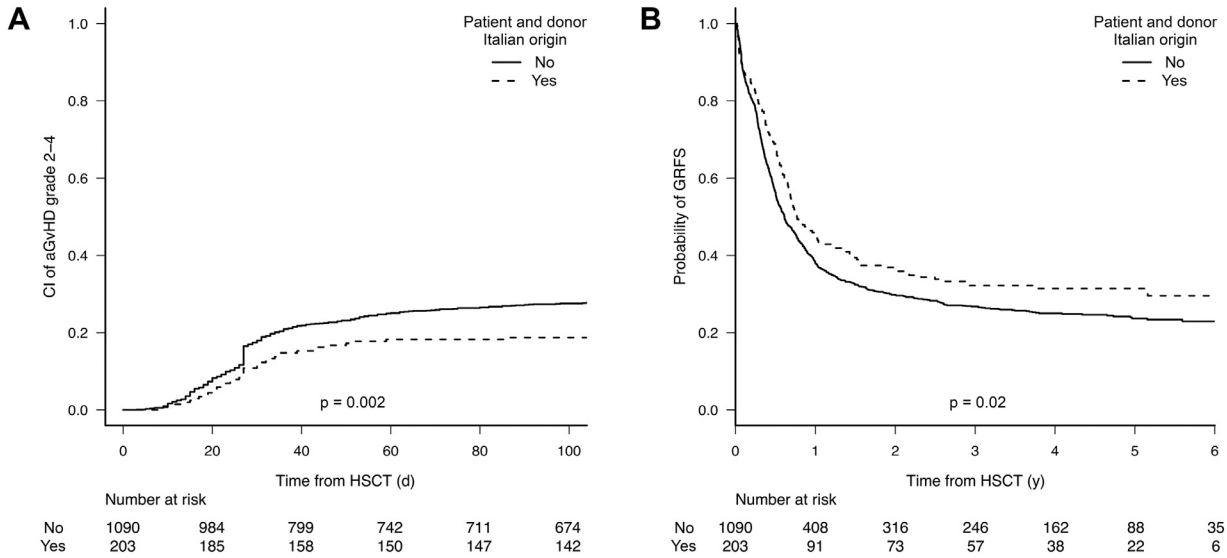

Figure 4. Outcome associations for patient and donor Italian origin in early and intermediate disease phases. (A) Cumulative incidence of grade II-IV aGVHD and (B) Kaplan-Meier probabilities for GRFS stratified for patient and donor Italian origin in early and intermediate disease phases.

805 Italian patients who underwent HSCT from an unrelated donor and found no difference in outcomes between low-resolution and high-resolution single incompatibility. In a GITMO-promoted study, Crocchiolo et al. [21] found a small, not statistically significant, survival difference between single HLA mismatching and 10/10 matched pairs regardless of the locus involved in the incompatibility, whereas 2 more mismatched HLA loci significantly affected OS and NRM. However, they found that HLA mismatch played a more significant role in the reduction of OS in the subgroup of patients undergoing HSCT with acute leukemia in first complete remission than in those with advanced disease (63% versus 54%).

Given the conflicting results reported in registry studies [5,9,11], and considering that 608 of the 805 patients in the GITMO study had advanced disease whereas 205 patients had chronic lymphoproliferative disorders [21], the GITMO, IBMDR, and AIBT analyzed a larger and more homogeneous cohort of patients, treated over a shorter period (3 years) compared with the study of Crocchiolo et al. (7 years). The present joint study shows that allelic mismatch had a statistically significant negative impact on the clinical outcomes of unrelated HSCT. Overall, compared with 10/10 HLA-compatible HSCT, each additional allelic disparity corresponded to progressively impaired results in terms of NRM and grade II-IV aGVHD. However, our previous data [30] reinforced the concept that a single HLA locus mismatch has similar advantages as 10/10-compatible transplantation in patients undergoing HSCT in an advanced stage of disease, except for a higher incidence of grade >II aGVHD, and without affecting NRM or OS. In contrast, increasing donor/recipient allelic disparity negatively

affected NRM, grade II-IV aGVHD, and OS in patients who underwent transplantation at an early or intermediate disease phase. As expected, the 4-year relapse incidence (44% versus 33%; $P = .0002$) was significantly higher in patients who underwent allogeneic HSCT at an advanced stage compared with those who did so at an early/intermediate stage. These results confirm disease status as a crucial factor in the success of transplantation and in the unmet clinical need for a preemptive strategy after allogeneic HSCT to reduce the risk of relapse.

In our analysis, allelic HLA compatibility was 10/10, 9/10, and ≤8/10 in 50%, 38%, and 12% of cases, respectively. The high proportion (50%) of patients undergoing allogeneic HSCT from a mismatched donor reflects the high HLA polymorphism of the Italian population, as reported previously [48]. The Italian Transplant Program preferably selects unrelated donors with incompatibility on single locus A, followed by loci C, B, and DQB1, and avoids DRB1 mismatching, thereby obtaining better HSCT results using single allelic HLA-C or -DQB1. In particular, single DQB1 mismatching does not seem to affect HSCT outcomes. Moreover, our results suggest that HLA-B incompatibility significantly affects HSCT outcomes by increasing the risks of aGVHD, cGVHD, relapse rate, and NRM, thereby reducing GRFS, whereas HLA-A mismatching significantly increases the 100-day cumulative incidence of grade II-IV aGVHD and reduces the 4-year probability of GRFS. Given the high rate of HLA-mismatched pairs and the interplay between HLA matching and the type of immunosuppressive regimen, we collected accurate data on GVHD prophylaxis. However, as reported in Supplementary Table S2, most patients (76%) received homogenous prophylaxis based on a combination of ATG, cyclosporine A, and a short course of methotrexate irrespective of HLA mismatch. Because only 2% of them received a combination that included post-transplantation cyclophosphamide as GVHD prevention, we were unable to carry out a subgroup analysis to test its performance activity in terms of reduced GVHD incidence, as reported recently [49,50].

Regarding non-HLA factors, we found that age ≥49 years, advanced disease and performance status (HCT-I or KPS) at transplantation are the main risk factors in terms of NRM, GRFS, PFS, and OS. We provide clinical evidence that recipient-donor pairs of Italian origin can be considered at a low risk of GVHD onset. It is feasible that HLA-matched and mismatched unrelated pairs of the same ethnic origin might benefit from a larger number of shared single nucleotide polymorphisms (SNPs) present in the extended major histocompatibility complex haplotypes. In this context, Petersdorf et al. [46] showed that HLA genes carrying SNPs belonging to the genotype of the donor or recipient may positively or negatively affect the clinical outcome of unrelated allogeneic HSCTs. However, data are scarce on the relationship between the quantity and the quality of SNPs involved in matched or mismatched unrelated allogeneic transplantations and the differing ancestry of the pairs. Madbouly et al. [47] reported that a high level of genetic admixture between transplant recipients and donors was associated with a high risk of overall mortality (HR, 2.26; $P = .005$ and HR, 3.09; $P = .0002$, respectively), transplantation-related mortality (HR, 3.3; $P = .0003$ and HR, 3.86; $P = .0001$, respectively), and decreased disease-free survival (HR, 1.9; $P = .02$ and HR, 2.46; $P = .002$, respectively) in an African subgroup, which suggests that a genetic driver can affect outcome. Our present findings and the aforementioned studies suggest that the ethnic origin of pairs may be considered an adjunctive prognostic factor, probably HLA-related, when selecting donors and encourage further investigations in this direction. Although limited by the inclusion of different hematologic malignancies, this study confirms that allelic HLA mismatch plays a crucial role in the outcome of HSCT and shows that the ethnic origin of pairs is a novel prognostic factor related to the clinical outcome in this setting.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jtct.2020.11.021.

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