Supplemental Information

Materials and Methods

Patients: The cohort examined was described in a previous study (5) with the exclusion of 4 transplants in which HLA typing for all LEL loci could not be performed in either the patient or the donor; the study included 3853 patients reported to the NMDP who underwent transplantation between 1988 and 2004 for acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic myeloid leukemia (CML), and myelodysplastic syndrome (MDS). Early-stage disease was defined as AML and ALL in first complete remission, CML in first chronic phase, and MDS subtype refractory anemia (5). Intermediate-stage disease was AML or ALL in second or subsequent complete remission or in first relapse, and CML in accelerated phase or second chronic phase. Advanced-phase disease was AML in second or higher relapse or primary induction failure, CML in blast phase, MDS subtype refractory anemia with excess blasts or in transformation, or MDS, not otherwise classified. All patients received myeloablative conditioning regimens defined as "traditional" if single-dose total body irradiation (TBI) greater than 500 cGy or more than 800 cGy total in fractionated doses (with or without cyclophosphamide) or cyclophosphamide with at least 9.5 mg/kg busulfan. "Non-traditional" preparative regimens involved busulfan with a dose of at least 9.5 mg/kg without cyclophosphamide or melphalan with a dose greater than 150 mg/m^2. Patients undergoing conditioning regimens of lower intensity, second or subsequent transplants, or surviving patients who did not provide written informed consent to allow analysis of their clinical data or HLA typing of stored NMDP Research Repository samples were excluded.

Scoring of mismatches: a mismatch in two alleles was defined as at least one amino acid difference in the antigen recognition site (ARS) of the HLA molecule between the alleles of each locus of the patient and the donor. In HLA class I molecules the ARS comprises the alpha-1 and alpha-2 domains, while in HLA class II molecules the first domains of each subunit (alpha-1 and beta-1) define the ARS. The mismatches in the class II molecules were scored according to the variations in the alpha and beta subunits of the corresponding loci. Given the complexity of heterodimers from alleles at polymorphic loci and the complex haplotype structures in which some loci are missing while others are present, several ad hoc matching scores for these loci were developed and examined in the current manuscript. In exploratory analysis, we conducted alternative scoring of DQ and DP mismatches utilizing the counts of the number of potential DQ or DP heterodimers not shared by the patient and donor. Since both, the alpha and beta subunits are polymorphic; an individual heterozygous in both DQA1 and DQB1 loci may have up to four different DQ heterodimers. For HLA-DQ, the scoring took into account that some DQA1 subunits cannot pair with some DQB1 subunits and form stable DQ molecules. Therefore the mismatches in the DQ heterodimers were evaluated on the basis of DQ-heterodimers that can be actually exist in a stable form (34); no possible heterodimers formation was considered for pairs formed by the DQA1*01 polypeptides combined with polypeptides of DQB1*02, DQB1*03 and DQB1*04; similarly, no possible heterodimer formation was considered for DQA1*02, DQA1*03, DQA1*04, DQA1*05 and DQA1*06 combined with DQB1*05 and DQB1*06. No restrictions in pairing for alleles of DPA1 and DPB1 were included. The outcomes of transplant groups having different number of DQ and DP heterodimers were compared with each other and stratified according the criteria used to score DP and DP mismatches in previous studies.[4,5]

Supplemental Table 1. Classification of HLA mismatches scored in the GvH vector.
Characteristics of patients with AML, ALL, CML and MDS where donor/recipient pairs have high resolution typing for HLA-A, -B, -C, -DRB1, -DQ and -DP through the NMDP and where recipient received a myeloablative conditioning regimen

Variable	8/8 for HLA -A,-B,-C and -DRB1 in GvH direction N (%)	7/8 for HLA -A,-B,-C and -DRB1 in GvH direction N (%)	< 7/8 for HLA-A,-B,-C and -DRB1 in GvH direction N (%)
Number of patients	1896	985	972
Number of centers	105	101	94
Age, median (range), years	35 (<1-65)	31 (<1-65)	28 (<1-59)
Age at transplant			
< 10 y	172 (9)	118 (12)	141 (15)
11 – 20 y	203 (11)	158 (16)	187 (19)
21 – 30 y	334 (18)	175 (18)	188 (19)
31 – 40 y	472 (25)	219 (22)	227 (23)
41 – 50 y	492 (26)	230 (23)	180 (19)
Over 50 y	222 (12)	85 (9)	49 (5)
Race			
White	1763 (93)	858 (87)	717 (74)
Black	49 (3)	49 (5)	91 (9)
Hispanic	55 (3)	56 (6)	109 (11)
Other	29 (1)	22 (2)	55 (6)
Male sex	1070 (56)	541 (55)	572 (59)
Karnofsky prior to transplant $\geq$ 90	1370 (72)	711 (72)	707 (73)
Low Expression Loci - DQ, DP and DRB3/4/5			
6/6	417 (22)	178 (18)	144 (15)
5/6	806 (43)	378 (38)	319 (33)
4/6	573 (30)	332 (34)	341 (35)
< 4/6	100 (5)	97 (10)	168 (17)
Disease at transplant			
AML	510 (27)	297 (30)	248 (26)
ALL	424 (22)	251 (25)	277 (28)
CML	784 (41)	366 (37)	388 (40)
MDS	178 (9)	71 (7)	59 (6)

Supplemental Table 1: Continued.

Variable	8/8 for HLA -A,-B,-C and -DRB1 in GvH direction N (%)	7/8 for HLA -A,-B,-C and -DRB1 in GvH direction N (%)	< 7/8 for HLA-A,-B,-C and -DRB1 in GvH direction N (%)
Disease status at transplant			
Early	861 (45)	378 (38)	361 (37)
Intermediate	693 (37)	417 (42)	421 (43)
Advanced	338 (18)	188 (19)	188 (19)
Other	4 (<1)	2 (<1)	2 (<1)
Conditioning regimen - TBI based	1535 (81)	815 (83)	856 (88)
GVHD prophylaxis			
FK506± MTX ± MMF ± Steroids ± other	374 (20)	185 (19)	133 (14)
FK506 ± other	3 (<1)	6 (1)	3 (<1)
CsA + MTX ± other	1109 (58)	507 (51)	527 (54)
CsA ± other (No MTX)	71 (4)	29 (3)	36 (4)
MMF ± other	4 (<1)	1 (<1)	0
MTX ± other (No CSA)	13 (1)	6 (1)	12 (1)
T-cell depletion	320 (17)	249 (25)	261 (27)
Other	2 (<1)	2 (<1)	0
Graft type			
Bone marrow	1752 (92)	915 (93)	944 (97)
PBSC	144 (8)	70 (7)	28 (3)
Donor/recipient sex match			
Male/Male	736 (39)	330 (34)	315 (32)
Male/Female	460 (24)	235 (24)	199 (20)
Female/Male	334 (18)	211 (21)	257 (26)
Female/Female	366 (19)	209 (21)	201 (21)
Donor/recipient CMV match			
Negative/Negative	689 (36)	339 (34)	285 (29)
Negative/Positive	533 (28)	272 (28)	280 (29)
Positive/Negative	308 (16)	157 (16)	166 (17)
Positive/Positive	310 (16)	192 (19)	211 (22)
Unknown	56 (3)	25 (3)	30 (3)
Donor age, median (range), years	36 (18-60)	36 (19-59)	36 (18-60)

Supplemental Table 1: Continued.

Variable	8/8 for HLA -A,-B,-C and -DRB1 in GvH direction N (%)	7/8 for HLA -A,-B,-C and -DRB1 in GvH direction N (%)	< 7/8 for HLA-A,-B,-C and -DRB1 in GvH direction N (%)
Donor age			
18-29	491 (25)	245 (25)	256 (26)
30-39	752 (40)	379 (38)	355 (37)
40-49	524 (28)	277 (28)	296 (30)
50 and older	129 (7)	84 (9)	65 (7)
Time from dx to tx, months median (range)	11 (0.3-232)	13 (0.3-309)	15 (0.4-200)
Year of transplant			
1988	11 (1)	7 (1)	4 (<1)
1989	35 (2)	12 (1)	29 (3)
1990	52 (3)	20 (2)	33 (3)
1991	68 (4)	40 (4)	66 (7)
1992	96 (5)	48 (5)	72 (7)
1993	87 (5)	46 (5)	67 (7)
1994	141 (7)	69 (7)	72 (7)
1995	142 (7)	94 (10)	87 (9)
1996	148 (8)	86 (9)	98 (10)
1997	179 (9)	79 (8)	83 (9)
1998	170 (9)	82 (8)	81 (8)
1999	178 (9)	105 (11)	82 (8)
2000	213 (11)	99 (10)	89 (9)
2001	172 (9)	121 (12)	67 (7)
2002	173 (9)	58 (6)	34 (3)
2003	31 (2)	19 (2)	8 (1)
Median follow-up of survivors, months	73 (3-194)	63 (6-191)	85 (4-192)

Note: Data is adjusted for the NMDP corrective action plan.[4,5]

Abbreviations: acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic myeloid leukemia (CML), and myelodysplastic syndrome (MDS); CMV, cytomegalovirus.

Supplemental Table 2. Comparisons of TRM in the multivariate model of HLA mismatches scored in the GvH vector at the HEL (HLA-A, B, C, DRB1) and LEL (DRB3/4/5, DQ, DP) HLA loci.

Comparisons between 7/8 and 8/8 groups	RR	Confidence Interval		p
8/8 0 LEL mismatch				
7/8 HEL, 0 LEL vs. 8/8 HEL, 0 LEL	1.45	1.11	1.90	**0.0059**
7/8 HEL, 1 LEL vs. 8/8 HEL, 0 LEL	**1.58**	**1.28**	**1.95**	**<0.0001**
7/8 HEL, 2 LEL vs. 8/8 HEL, 0 LEL	**1.74**	**1.40**	**2.16**	**<0.0001**
8/8 1 LEL mismatch				
7/8 HEL, 0 LEL vs. 8/8 HEL, 1 LEL	1.23	0.96	1.56	0.0954
7/8 HEL, 1 LEL vs. 8/8 HEL, 1 LEL	**1.34**	**1.12**	**1.59**	**0.0013**
7/8 HEL, 2 LEL vs. 8/8 HEL, 1 LEL	**1.47**	**1.22**	**1.76**	**<0.0001**
8/8 2 LEL mismatches				
7/8 HEL, 0 LEL vs. 8/8 HEL, 2 LEL	1.15	0.90	1.47	0.2660
7/8 HEL, 1 LEL vs. 8/8 HEL, 2 LEL	**1.25**	**1.04**	**1.51**	**0.0176**
7/8 HEL, 2 LEL vs. 8/8 HEL, 2 LEL	**1.38**	**1.14**	**1.67**	**0.0010**
8/8 >2 LEL mismatches				
7/8 HEL, 0 LEL vs. 8/8 HEL, >2 LEL	1.09	0.76	1.55	0.6529
7/8 HEL, 1 LEL vs. 8/8 HEL, >2 LEL	1.18	0.86	1.62	0.3009
7/8 HEL, 2 LEL vs. 8/8 HEL, >2 LEL	1.30	0.94	1.79	0.1087

Comparisons within 7/8 groups	RR	Confidence Interval		p
7/8 >2 LEL mismatches				
7/8 HEL, >2 LEL vs. 8/8 HEL, 2 LEL	1.37	1.02	1.83	0.0383
7/8 HEL, >2 LEL vs. 8/8 HEL, 1 LEL	**1.50**	**1.12**	**2.01**	**0.0063**
7/8 HEL, >2 LEL vs. 8/8 HEL, 0 LEL	**1.63**	**1.17**	**2.28**	**0.0039**
7/8 with 0, 1 and 2 LEL mismatches				
7/8 HEL, 2 LEL vs. 7/8 HEL, 0 LEL	1.20	0.92	1.55	0.1769
7/8 HEL, 2 LEL vs. 7/8 HEL, 1 LEL	1.10	0.90	1.35	0.3659
7/8 HEL, 1 LEL vs. 7/8 HEL, 0 LEL	1.09	0.84	1.41	0.5165

In bold are shown statistically significant different comparisons.