Impact of graft composition on outcomes of haploidentical bone marrow stem cell transplantation

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SUPPLEMENTAL MATERIAL

Supplemental material 1. Study methods

Graft composition assessment

Immunophenotyping was performed on fresh BM donor graft samples. BM mononuclear cells were surface-stained with monoclonal antibodies against CD34, CD3, CD4, CD8, CD19, and CD56 antigens using 7-AAD in MDCC flow cytometer lab. Total nucleated cell (TNC) dose was assessed by using a white blood cell count from an automated hematology analyzer. The device counts white blood cells using flow cytometry with a semiconductor laser exploiting the differences in cell size, complexity, and RNA/DNA content.

Outcomes and statistical analysis

Study endpoints included early (≤60 days after transplant) and late (>60 days after transplant) non-relapse mortality (NRM), severe (grade III or IV) acute GVHD (aGVHD), disease progression, and progression-free survival (PFS). Univariate analysis using Cox proportional hazards regression analysis and Fine and Gray competing-risks regression was used to evaluate donor, recipient, disease, and transplant characteristics and graft cellular characteristics (including CD34+, TNC, CD3+CD4+, CD3+CD8+, CD3+CD4+/CD3+CD8+, CD19+, and CD3-CD56+ cell populations) for associations with outcomes.

Predictors that were significant at the 0.1 level on univariate analysis were considered for multivariate analysis using Classification And Regression Tree (CART) analysis to classify donor, recipient, and graft characteristics in order of their statistical impact and identify interaction effects among these three categories of predictors. This method was used because it accommodates potential correlations and interaction effects, and provides a platform for development of algorithms for donor selection. CART is a machine-learning

method used to generate prognostic algorithms. These algorithms are developed through a recursive partitioning process that interrogates the predictive value of each factor included in the analysis and partitions the data based on the most significant predictors. This process is repeated within each partition until no additional significant predictors are identified. The result of this process is depicted in a decision tree figure in which only factors that are statistically significant predictor of the outcome are represented. Factors that are not depicted in the decision tree would not have additional predictive value. For this analysis, we set the statistical significance at the 0.1 level, and we required a minimal sample size of 10 patients for each terminal partition.

Supplemental material 2. Patients characteristics of training and validation cohort

	Training cohort **N=147**	**Validation** cohort **N=111**	***P** value*
Graft Characteristics			
CD4/CD8, median [IQRT]	1.1 [0.85-1.5]	1.2 [0.9, 1.7]	0.4
≤0.85	37 (25)	20 (18)	0.2
>1.5	35 (24)	32 (29)	0.4
% CD4	40 [35, 46]	39 [32, 46]	0.15
% CD8	35 [30, 42]	31 [27, 38]	<0.001
% CD19	9 [6, 13]	12 [9, 18]	<0.001
% CD56	9 [6, 12]	10 [8, 12]	<0.001
Donor Characteristics			
Donor age, years			
Median (range)	35 (14-85)	34 (12-66)	0.2
>30	88 (60)	65 (59)	0.8
>50	27 (18)	14 (13)	0.2
Donor gender			0.05

Female	65 (44)	36 (32)	
Male	82 (56)	75 (68)	
Donor gender / age			
Male ≤ 30 y	35 (24)	30 (27)	
Female ≤30 y	24 (16)	16 (14)	
Female >30 y	41 (28)	20 (18)	0.06
Male >30 y	47 (32)	45 (40)	
Donor/Recipient gender			
Female/Male	38 (26)	16 (14)	0.02
Female/Female	27 (18)	20 (18)	
Male/Female	34 (23)	34 (31)	
Male/Male	48 (33)	41 (37)	
Donor CMV			0.06
R	94 (64)	58 (52)	
NR	53 (36)	53 (48)	
Donor/Recipient CMV			
R/R	86 (59)	53 (48)	
R/NR	8 (6)	5 (5)	
NR/R	42 (29)	42 (38)	0.1
NR/NR	9 (6)	11 (10)	
Donor relation			
Child	60 (41)	61 (55)	0.02
Parent	18 (12)	8 (7)	
Sibling	67 (46)	40 (36)	
Other	2 ()	2 (2)	
Recipient and disease characteristics			
Recipient age, years			
Median (range)	47 (18-69)	52 (19-72)	0.03
≤60	120 (82)	86 (78)	

>60	27 (18)	25 (22)	0.4
Recipient HCT-CI			
≤3	107 (73)	73 (66)	
>3	40 (27)	38 (34)	0.2
Diagnosis			0.4
AML/MDS	80 (54)	71 (64)	
ALL	26 (18)	20 (18)	
CML/MPD	19 (13)	6 (5)	
CLL	5 (3)	4 (4)	
Lymphoma	10 (7)	5 (4)	
Hodgkin lymphoma	6 (4)	4 (4)	
Aplastic anemia	1 (1)	0	
Disease Risk Index			
Very high	10 (7)	11 (10)	
High	51 (35)	51 (46)	0.02
Intermediate	62 (42)	41 (37)	
Low	23 (16)	8 (7)	

Supplemental material 3. Summary of outcomes 3 years after transplant, unless otherwise indicated

Outcome	Nr of events	Median time to event (range)	Cumulative incidence (%)	95% CI
Day +180 severe aGVHD	16	40 days (21-180)	11	7-17
Early (day +60 or before) NRM	6	29 days (7-59)	4	2-9
Late (after day +60) NRM	32	4 months (2.3-35)	24	17-32
Disease progression	40	6 months (1.4-27)	28	21-36
Progression-free survival	79	5 months (0.2-35)	45	36-53

Supplemental material 4. Evaluation of donor and recipient characteristics as predictors of transplant outcomes 3 years after transplant, unless otherwise indicated

	Severe aGVHD		Day +60 NRM		NRM		Disease progression		PFS	
Characteristic	**HR**	***P***	**HR**	***P***	**HR**	***P***	**HR**	***P***	**HR**	***P***
Donor age, years										
>30 vs ≤30	5	0.03	0.7	0.6	2.1	0.06	0.6	0.1	1.03	0.9
>50 vs ≤50	1	0.9	2.3	0.3	2.1	0.05	0.45	0.1	1.3	0.2
>60 vs ≤60	1.8	0.5	NE	0.6	0.8	0.9	0.6	0.6	1.3	0.4
Donor gender										
Female	9.8	0.003	0.6	0.6	1.7	0.1	0.6	0.1	1.04	0.8
Male	Ref.		Ref.		Ref.		Ref.		Ref.	
Donor/Recipient gender										
Female/Male	5.4	0.03	NE	0.2	1.2	0.6	0.9	0.9	0.9	0.9
Female/Female	6.1	0.03	1.7	0.6	1.5	0.4	0.5	0.2	0.9	0.9
Male/Female	NE		1.4	0.7	0.5	0.3	1.5	0.3	1.1	0.8
Male/Male	Ref.		Ref.		Ref.		Ref.		Ref.	
Donor CMV										
R	4.2	0.06	1.1	0.9	2.2	0.06	0.5	0.06	1	0.9
NR	Ref.		Ref.		Ref.		Ref.		Ref.	
Donor/Recipient ABO incompatibility										
Major	1.7	0.5	2.4	0.4	1.4	0.6	0.8	0.7	1.2	0.6
None/Minor	Ref.		Ref.		Ref.		Ref.		Ref.	
Recipient age, years										
>30 vs ≤30	0.7	0.6	NE	0.1	1.7	0.2	0.45	0.01	0.9	0.7
>60 vs ≤60	2	0.2	0.9	0.9	2.3	0.03	0.6	0.3	1.3	0.4
Recipient HCT-CI										

≤3	Ref.		Ref.		Ref.		Ref.		Ref.	
>3	1.6	0.4	1.3	0.7	2.05	0.04	0.6	0.2	1.3	0.3
DRI										
Very High/High	1.1	0.9	0.7	0.7	1.3	0.5	6.4	<0.001	3.1	<0.001
Intermediate/Low	Ref.		Ref.		Ref.		Ref.			