

Supplementary information for

Deletion of Y-chromosome before allogeneic hematopoietic stem cell transplantation in male recipients with female donors.

Masaharu Tamaki^{1, 17#}, Kazuaki Kameda^{1,17}, Shun-ichi Kimura^{1,17}, Naonori Harada^{2,17}, Naoyuki Uchida³, Noriko Doki⁴, Masatsugu Tanaka⁵, Kazuhiro Ikegame⁶, Masashi Sawa⁷, Yuta Katayama⁸, Shigesaburo Miyakoshi⁹, Takahide Ara¹⁰, Junya Kanda¹¹, Makoto Onizuka¹², Takahiro Fukuda¹³, Yoshiko Atsuta^{14,15}, Yoshinobu Kanda¹, Kimikazu Yakushijin^{16,17}, Hideki Nakasone^{1,17#} .

1. Division of Hematology, Jichi Medical University Saitama Medical Center, Saitama, Japan
2. Department of Hematology, Graduate School of Medicine, Osaka City University, Osaka, Japan
3. Department of Hematology, Federation of National Public Service Personnel Mutual Aid Associations Toranomon Hospital, Tokyo, Japan
4. Hematology Division, Tokyo Metropolitan Cancer and Infectious Disease Center, Komagome Hospital, Tokyo, Japan
5. Department of Hematology, Kanagawa Cancer Center, Yokohama, Japan
6. Department of Hematology, Hyogo College of Medicine Hospital, Nishinomiya, Japan
7. Department of Hematology and Oncology, Anjo Kosei Hospital, Anjo, Japan
8. Department of Hematology, Hiroshima Red Cross Hospital & Atomic-bomb Survivors Hospital, Hiroshima, Japan
9. Department of Hematology, Tokyo Metropolitan Geriatric Hospital, Tokyo, Japan
10. Department of Hematology, Hokkaido University Hospital, Sapporo, Japan
11. Department of Hematology and Oncology, Graduate School of Medicine, Kyoto University, Kyoto, Japan
12. Department of Hematology / Oncology, Tokai University School of Medicine, Isehara, Japan
13. Hematopoietic Stem Cell Transplantation Division, National Cancer Hospital, Tokyo, Japan
14. Japanese Data Center for Hematopoietic Cell Transplantation, Nagoya, Japan
15. Department of Registry Science for Transplant and Cellular Therapy, Aichi Medical University School of Medicine, Nagakute, Japan
16. Department of Medical Oncology and Hematology, Kobe University Hospital, Kobe, Japan
17. Transplant Complications Working Group of Japanese Society for Transplantation and Cellular therapy (JSTCT)

Co-corresponding authors:

Masaharu Tamaki, M.D. E-mail: mtamaki@jichi.ac.jp

Hideki Nakasone, M.D., Ph.D. E-mail: nakasone-tyk@umin.ac.jp

Division of Hematology, Jichi Medical University Saitama Medical University Saitama Medical Center, 1-847 Amanuma-cho, Omiya-ku, Saitama city, Saitama 330-8503

E-mail: mtamaki@jichi.ac.jp

TEL: +81-48-647-2111 FAX: +81-48-644-5166

Supplemental Tables

Supplemental Table 1. Multivariate analysis of acute GVHD and chronic GVHD in female-to-male transplant recipients.

		Grade II - IV acute GVHD		Chronic GVHD	
		HR (95% CI)	P	HR (95% CI)	P value
Del (Y)		1.18 (0.890 – 1.56)	0.25	0.819 (0.576 – 1.16)	0.27
Age > 50 years		0.978 (0.867 – 1.10)	0.72	1.13 (1.00 – 1.28)	0.046
Disease	AML	Reference	1.0	Reference	1.0
	ALL	1.09 (0.945 – 1.26)	0.23	0.856 (0.739 – 0.993)	0.040
	MDS	1.11 (0.965 – 1.28)	0.14	1.09 (0.939 – 1.26)	0.26
	MPN	0.908 (0.663 – 1.24)	0.55	1.02 (0.750 – 1.37)	0.92
DRI	Low	Reference	1.0	Reference	1.0
	Intermediate	0.965 (0.729 – 1.28)	0.80	0.954 (0.732 – 1.24)	0.73
	High	1.06 (0.800 – 1.41)	0.67	0.931 (0.707 – 1.23)	0.61
	Very high	0.924 (0.657 – 1.30)	0.65	0.680 (0.458 – 1.01)	0.056
HCT-CI \geq 2		1.11 (0.988 – 1.25)	0.078	1.07 (0.945 – 1.22)	0.28
PS 2 – 4		0.985 (0.802 – 1.21)	0.89	0.895 (0.685 – 1.17)	0.42
Donor type	Matched related	Reference	1.0	Reference	1.0
	Matched unrelated	1.22 (0.983 – 1.52)	0.072	1.08 (0.879 – 1.32)	0.47
	Mismatched related	1.11 (0.888 – 1.39)	0.36	0.795 (0.631 – 1.00)	0.051
	Mismatched	1.36 (1.07 – 1.73)	0.012	1.04 (0.826 – 1.31)	0.74
Donor source	Bone marrow	Reference	1.0	Reference	1.0
	Peripheral blood	1.18 (0.985 – 1.42)	0.072	1.09 (0.923 – 1.29)	0.31
	Cord blood	0.963 (0.808 – 1.15)	0.67	0.546 (0.452 – 0.659)	<0.001
Myeloablative conditioning		1.17 (1.03 – 1.33)	0.016	1.46 (1.27 – 1.68)	<0.001
GVHD prophylaxis	CsA-based	Reference	1.0	Reference	1.0
	TAC-based	0.856 (0.747 – 0.981)	0.025	0.906 (0.787 – 1.04)	0.17
	Others	0.814 (0.522 – 1.27)	0.36	0.970 (0.623 – 1.51)	0.89
in vivo T cell depletion		0.961 (0.795 – 1.16)	0.68	0.794 (0.643 – 0.892)	0.033

Abbreviations: Del(Y), deletion of Y-chromosome; GVHD, graft-versus-host disease; HR, hazard ratio; CI, confidence interval; AML, acute myeloid leukemia; ALL, acute lymphoid leukemia; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm; DRI, disease risk index; HCT-CI, hematopoietic cell transplantation comorbidity index; PS, performance status; CsA, cyclosporine; TAC, tacrolimus

Supplemental Table 2. Main cause of death.

	Del(Y) (n = 155)	Y-present (n = 4149)	P value
Progression	51 (32.9)	790 (19.0)	<0.001
Infection	13 (8.4)	414 (10.0)	0.59
Acute GVHD	2 (1.3)	87 (2.1)	0.77
TMA	4 (2.6)	57 (1.4)	0.28
SOS	2 (1.3)	52 (1.3)	0.72
Graft failure	0 (0.0)	50 (1.2)	0.26

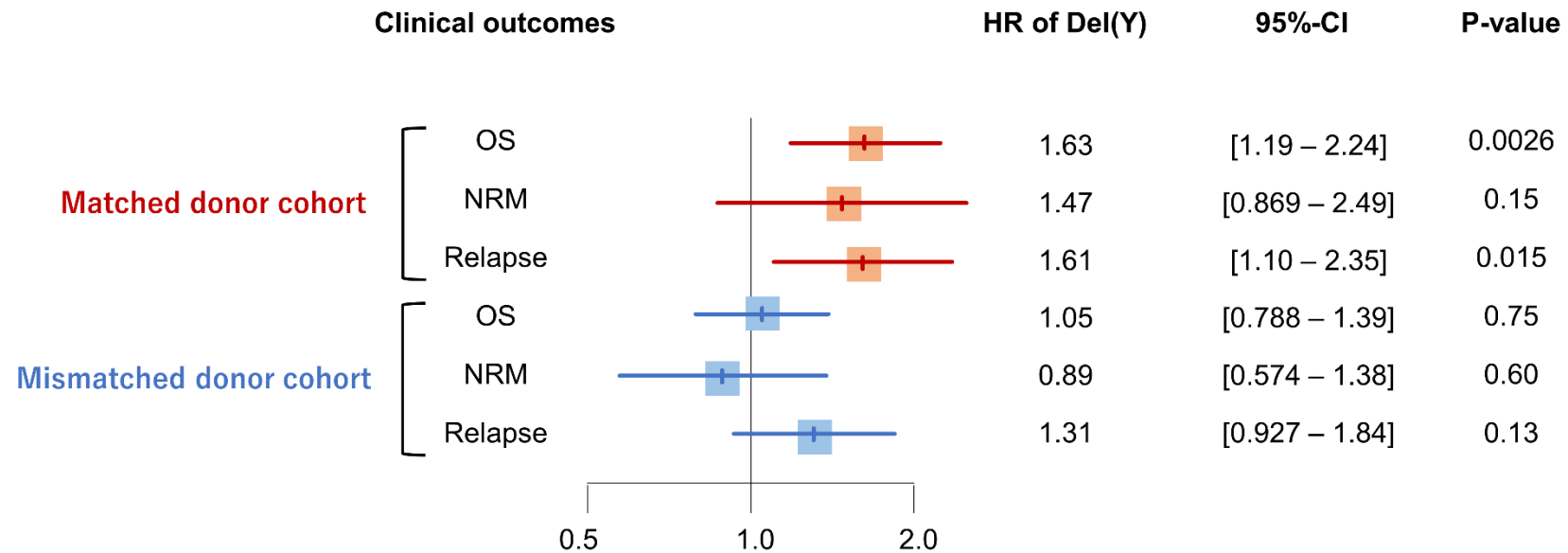
Abbreviations: Del(Y), deletion of Y-chromosome; Y-present, presence of Y-chromosome; GVHD, graft-versus-host disease; TMA, thrombotic microangiopathy; SOS, sinusoidal obstruction syndrome.

Supplemental Table 3. Patient characteristics in a matched-pair analysis.

		Female-to-male allo-HCT		Male-to-male allo-HCT	
		Del(Y) (n = 117)	Y-present (n = 117)	Del(Y) (n = 194)	Y-present (n = 194)
Age, n (%)	≤ 50 years	40 (34.1)	40 (34.1)	76 (39.2)	76 (39.2)
	> 50 years	77 (67.5)	77 (67.5)	118 (60.8)	118 (60.8)
Disease type, n (%)	AML	83 (70.9)	83 (70.9)	124 (63.9)	124 (63.9)
	ALL	13 (11.1)	13 (11.1)	22 (11.3)	22 (11.3)
	MDS	21 (17.9)	21 (17.9)	46 (23.7)	46 (23.7)
	MPN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
DRI, n (%)	Low	15 (12.8)	15 (12.8)	21 (10.8)	21 (10.8)
	Intermediate	39 (33.3)	39 (33.3)	91 (46.9)	91 (46.9)
	High	37 (31.6)	37 (31.6)	52 (26.8)	52 (26.8)
	Very high	26 (22.2)	26 (22.2)	30 (15.5)	30 (15.5)
HCT-CI, n (%)	0 – 1	69 (59.0)	69 (59.0)	119 (61.3)	119 (61.3)
	≥ 2	48 (41.0)	48 (41.0)	75 (38.7)	75 (38.7)
PS, n (%)	0 – 1	108 (92.3)	108 (92.3)	180 (92.8)	180 (92.8)
	2 – 4	9 (7.7)	9 (7.7)	14 (7.2)	14 (7.2)
Donor type, n (%)	Matched related	25 (21.4)	25 (21.4)	32 (16.5)	32 (16.5)
	Matched unrelated	19 (16.2)	19 (16.2)	57 (29.4)	57 (29.4)
	Mismatched related	8 (6.8)	8 (6.8)	17 (8.8)	17 (8.8)
	Mismatched unrelated	65 (55.6)	65 (55.6)	88 (45.4)	88 (45.4)
Donor source, n (%)	Bone marrow	31 (26.5)	31 (26.5)	82 (42.3)	82 (42.3)
	Peripheral blood	29 (24.8)	29 (24.8)	50 (25.8)	50 (25.8)
	Cord blood	57 (48.7)	57 (48.7)	62 (32.0)	62 (32.0)
Conditioning regimen, n (%)	MAC	78 (66.7)	78 (66.7)	145 (74.7)	145 (74.7)
	RIC	39 (33.3)	39 (33.3)	49 (25.3)	49 (25.3)
GVHD prophylaxis, n (%)	CsA-based	26 (22.2)	26 (22.2)	48 (24.7)	48 (24.7)
	TAC-based	89 (76.1)	89 (76.1)	144 (74.2)	144 (74.2)
	Other	2 (1.7)	2 (1.7)	2 (1.0)	2 (1.0)
in vivo T-cell depletion, n (%)	+	112 (95.7)	112 (95.7)	182 (93.8)	182 (93.8)
	-	5 (4.3)	5 (4.3)	12 (6.2)	12 (6.2)

Abbreviations: Del(Y), deletion of Y chromosome; Y-present, presence of Y-chromosome; AML, acute myeloid leukemia; ALL, acute lymphoid leukemia; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm; DRI, disease risk index; HCT-CI, hematopoietic cell transplantation comorbidity index; PS, performance status; MAC, myeloablative conditioning; RIC, reduced intensity conditioning; GVHD, graft-versus-host disease; CsA, cyclosporine; TAC, tacrolimus.

Supplemental Figure 1. Impact of deletion of Y-chromosome (Del(Y)) on clinical outcomes allogeneic hematopoietic cell transplantation from female donors to male recipients (female-to-male allo-HCT) in the sub cohorts stratified according to HLA disparity.



Supplemental Figure 2. Impact of female-to-male allo-HCT in the sub cohorts stratified according to the presence of Y-chromosome.

