Clinical outcomes of three haploidentical transplantation protocols for hematologic malignancies based on data from the Chinese Bone Marrow Transplantation Registry Group

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Methods

Study endpoints and definitions

The primary study endpoint was leukaemia-free survival (LFS). The secondary study endpoints included engraftment, acute GvHD (aGvHD), cytomegalovirus (CMV) viraemia, Epstein–Barr virus (EBV) viraemia, relapse, NRM and OS. LFS was defined as the duration from transplantation to either death or relapse, depending on which occurred first. Neutrophil engraftment was defined as an absolute neutrophil count (ANC) in peripheral blood (PB) of ≥ 0.5×10^9/L for three consecutive days, and platelet engraftment was defined as a platelet count of ≥ 20×10^9/L for seven consecutive days in the absence of platelet transfusion. aGVHD was defined and graded according to the modified Seattle–Glucksberg criteria. Using real-time quantitative PCR to detect the copy numbers of CMV-DNA and EBV-DNA in PB, a CMV-DNA count exceeding 5×10^2/L was diagnosed as CMV viraemia, and an EBV-DNA count exceeding 1×10^3/L was diagnosed as EBV viraemia. Relapse was defined as the presence of ≥5% bone marrow (BM)

blasts or the reappearance of extramedullary leukaemia after complete remission (CR). NRM was defined as the incidence of death due to causes other than relapse or disease progression. OS was defined as the duration from transplantation to death due to any cause or to the time at which survival was confirmed.

Statistical analysis

The data were updated until April 30, 2024. Death was considered the competing risk for engraftment and GvHD, whereas relapse and NRM were competing risks for each other. Hazard ratios (HRs) for OS and LFS were estimated from univariate and multivariate Cox regression analyses. HRs for engraftment, aGvHD, relapse, and NRM were estimated from univariate and multivariate competing risk regression analyses. The factors included in the regression model were patient age, sex, disease type, disease risk index (DRI), HCT-CI score, donor–recipient relationship, donor–recipient sex match, donor–recipient ABO match status, source of stem cells, mononuclear cell (MNC) count, CD34+ cell count, and transplant protocol. All of the factors with $P < 0.1$ in the univariate analysis were included in the multivariate regression.

Supplementary Table 1. Baseline patient characteristics and clinical outcomes between PTCy and PTCy with ATG group.

Characteristics	PTCy group (n=122)	PTCy+ATG^{low} group (n=123)	P value
Median age at allo-HSCT, years (range)	31 (3–60)	34 (2–60)	0.478
Sex, n (%)			0.479
Male	55 (45.1%)	61 (49.6%)	
Female	67 (54.9%)	62 (50.4%)	
Diagnosis, n (%)			0.176
AML	62 (50.8%)	61 (49.6%)	
ALL	35 (28.7%)	47 (38.2%)	
MDS	15 (12.3%)	11 (8.9%)	
Others	10 (8.2%)	4 (3.3%)	
Disease risk index, n (%)			0.132
Low risk	4 (3.3%)	2 (1.6%)	
Intermediate + high risk	111 (91.0%)	119 (96.7%)	
Very high risk	7 (5.7%)	2 (1.6%)	
HCT-CI, n (%)			0.250
0	37 (30.3%)	26 (21.1%)	
1–2	78 (63.9%)	88 (71.5%)	
≥3	7 (5.7%)	9 (7.3%)	
Number of HLA-A/B/DRB1 mismatches, n (%)			

0–2			
3			
Donor-patient sex match, n (%)			0.265
Male-male	37 (30.3%)	39 (31.7%)	
Male-female	47 (38.5%)	35 (28.5%)	
Female-male	15 (12.3%)	24 (19.5%)	
Female-female	23 (18.9%)	25 (20.3%)	
Donor-recipient relationship, n (%)			**0.047**
Parents-child	43 (35.2%)	42 (34.1%)	
Child-parents	34 (27.9%)	50 (40.7%)	
Sibling-sibling	44 (36.1%)	28 (22.8%)	
Others	1 (0.8%)	3 (2.4%)	
ABO match, n (%)			0.098
Match	76 (62.3%)	73 (59.3%)	
Minor mismatch	21 (17.2%)	20 (16.3%)	
Major mismatch	17 (13.9%)	28 (22.8%)	
Bidirectional mismatch	8 (6.6%)	2 (1.6%)	
MNCs ($\times 10^8$/kg), median (range)	11.05 (3.58–34.63)	11.91 (5.60–31.94)	0.103
$CD34^+$ cells ($\times 10^6$/kg), median (range)	6.07 (2.30–17.88)	5.60 (0.52–17.30)	0.139
Graft resource, n (%)			0.233

BM+PB cell	1 (0.8%)	0	
PB cell	121 (99.2%)	123 (100%)	
Neutrophil engraftment	97.5% (94.5–100%)	100%	**0.003**
Platelet engraftment	84.4% (77.9–90.9%)	82.9% (76.2–89.7%)	0.281
aGvHD24	28.7% (20.7–36.8%)	27.9% (19.9–35.9%)	0.928
aGvHD34	13.1% (7.1–19.2%)	14.8% (8.4–21.1%)	0.694
3-year cGvHD	28.3% (18.9–37.6%)	24.5% (15.2–33.8%)	0.611
3-year moderate and severe cGvHD	10.6% (3.7–17.5%)	8.1% (2.7–134.4%)	0.900
CMV viremia	65 (53.3%)	71 (57.7%)	0.484
EBV viremia	17 (13.9%)	24 (19.5%)	0.242
3-year CIR	10.9% (5.3–16.6%)	9.0% (3.9-14.0%)	0.644
3-year NRM	26.2% (18.1-34.3%)	27.6% (19.7-35.6%)	0.546
3-year OS	65.2% (57.0-74.7%)	64.8% (56.8-73.9%)	0.661
3-year LFS	62.9% (54.6-72.4%)	63.4% (55.4-72.5%)	0.741

ALL, acute lymphocytic leukemia; allo-HSCT, allogeneic hematopoietic stem cell transplantation; AML, acute myeloid leukemia; ATG, antithymocyte globulin; BM, bone marrow; G-CSF, granulocyte colony-stimulating factor; GvHD, graft-versus-host disease; HCT-CI, hematopoietic cell transplantation-comorbidity index; MDS, myelodysplastic syndromes; MNCs, mononuclear cells; PB, peripheral blood; PTCy, posttransplantation cyclophosphamide.

Supplementary Table 2. The clinical outcomes among the three groups based on all patients enrolled in the study.

	G-CSF/ATG (n=309)	PTCy (n=122)	PTCy+ATG^{low} (n=123)	P value
3-year NRM	8.7% (5.6–11.9%)	26.2% (18.1–34.3%)	27.6% (19.7–35.6%)	<0.001
3-year CIR	14.5% (10.4–18.7%)	10.9% (5.3–16.6%)	9.0% (3.9–14.0%)	0.426
3-year OS	83.6% (79.5–87.8%)	65.2% (57.0-74.7%)	64.8% (56.8–73.9%)	<0.001
3-year LFS	76.7% (72.0–81.8%)	62.9% (54.6–72.4%)	63.4% (55.4–72.5%)	<0.001
Neutrophil engraftment at day28	98.7% (97.4–100%)	97.5% (94.5–100%)	100%	0.026
Platelet engraftment at day100	92.9% (90.0–95.8%)	84.4% (77.9–90.9%)	82.9% (76.2–89.7%)	0.009
Grades II-IV aGvHD at day100	27.8% (22.9–32.8%)	28.7% (20.7–36.8%)	27.9% (19.9–35.9%)	0.989
Grades III-IV aGvHD at day100	11.7% (8.1–15.2%)	13.1% (7.1–19.2%)	14.8% (8.4–21.1%)	0.604
3-year cGvHD	34.4% (28.8–40.1%)	28.3% (18.9–37.6%)	24.5% (15.2–33.8%)	0.159
3-year moderate and severe	15.6% (11.3–20.0%)	10.6% (3.7–17.5%)	8.1% (2.7–134.4%)	0.136
PTLD	6 (1.9%)	2 (1.6%)	1 (0.8%)	0.828
CMV	177 (57.3%)	65 (53.3%)	71 (57.7%)	0.716
EBV	44 (14.2%)	17 (13.9%)	24 (19.5%)	0.346

ATG, antithymocyte globulin; aGvHD, acute graft-versus-host disease; cGvHD, chronic graft-versus-host disease; G-CSF, granulocyte colony-stimulating factor; LFS, leukemia-free survival; NRM, non-relapse mortality; OS, overall survival; PTLD, Posttransplant lymphoproliferative disorders; PTCy, posttransplantation cyclophosphamide.

Supplementary Table 3. Multivariate analysis of risk factors for relapse, NRM, OS and LFS in G-CSF/ATG group, PTCy group and PTCy with ATG group.

Variables	Relapse		NRM		OS		LFS	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Patient age	/	/	1.02 (1.00-1.04)	0.058	1.01 (1.00–1.02)	0.22	/	/
High/very high vs.	2.55 (1.45–4.49)	**0.001**	3.04 (1.75–5.32)	**<0.001**	2.16 (1.50–3.11)	**<0.001**	2.39 (1.72–3.31)	**<0.001**
HCT-CI>0 vs. HCT-CI=0	/	/	1.25 (0.66–2.37)	0.49	1.40 (0.89–2.21)	0.141	11.29 (0.90–1.85)	0.160
Others vs. parent-child	0.62 (0.35-1.09)	0.10	/	/	/	/	/	/
≥$10*10^8$ vs. <$10*10^8$ MNCs	/	/	/	/	1.07 (0.74–1.55)	0.728	/	/
≥$4*10^6$ vs. <$4*10^6$ $CD34^+$ cells	0.55 (0.31–0.96)	**0.037**	0.86 (0.47–1.55)	0.49	/	/	/	/
PTCy-based vs. G-CSF/ATG-	/	/	2.59 (1.30–5.12)	**0.007**	1.94 (1.24–3.04)	**0.004**	1.46 (0.99–2.15)	0.057
PTCy+ATG^{low} based vs. G-			2.56 (1.24–5.26)	**0.011**	2.12 (1.36-3.30)	**<0.001**	1.56 (1.06–2.30)	**0.024**

ATG, antithymocyte globulin; CI, confidence interval; DRI, disease risk index, G-CSF, granulocyte colony-stimulating factor; HCT-CI, hematopoietic cell transplantation-comorbidity index, HR, hazard ratio; LFS, leukemia-free survival; MNCs, mononuclear cells; NRM, non-relapse mortality; OS, overall survival; PTCy, posttransplantation cyclophosphamide.

Supplementary Table 4. Multivariate analysis of risk factors for engraftment, aGvHD and cGvHD in G-CSF/ATG group, PTCy group and PTCy with ATG group.

Variables	Neutrophil engraftment		Platelet engraftment		Grade 2-4 aGvHD		Grade 3-4 aGvHD	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Female vs. male for patient	/	/	1.14 (0.96–1.35)	0.14	/	/	0.69 (0.41–1.16)	0.16
ALL vs. AML	/	/	0.69 (0.57–0.84)	**<0.001**	/	/	1.14 (0.64–2.03)	0.66
MDS vs. AML	/	/	0.73 (0.55–0.98)	**0.038**	/	/	2.17 (1.11–4.24)	**0.023**
Others vs. AML	/	/	0.68 (0.48–0.95)	**0.025**	/	/	2.58 (1.21–5.48)	**0.014**
High/very high vs.	0.78 (0.64–0.95)	**0.013**	0.79 (0.66–0.95)	**0.011**	1.62 (1.18–2.24)	**0.003**	1.90 (1.18–3.06)	**0.008**
HCT-CI>0 vs. HCT-CI=0	/	/	0.88 (0.74–1.05)	**0.015**	/	/	/	/
Others vs female-male. in	/	/	1.25 (0.94–1.66)	0.13	/	/	0.76 (0.40–1.47)	0.42
≥4*10^6 vs. <4*10^6 $CD34^+$ cells	1.56 (1.28–1.90)	**<0.001**	/	/	/	/	/	/
PTCy-based vs. G-CSF/ATG-	0.54 (0.42–0.69)	**<0.001**	0.76 (0.62–0.93)	**0.009**	/	/	/	/
PTCy+ATG^{low} based vs. G-	0.81 (0.64–1.02)	0.068	0.87 (0.69–1.10)	0.24	/	/	/	/

Variables	cGvHD		Moderate and severe cGvHD	
	HR (95% CI)	P value	HR (95% CI)	P value
Patient age	1.01 (0.99–1.02)	0.34	/	/
High/very high vs. low/intermediate risk of DRI	1.54 (1.10–2.15)	**0.013**	1.70 (1.01–2.84)	**0.046**

HCT-CI>0 vs. HCT-CI=0	1.29 (0.88–1.89)	0.18	/	/
PTCy-based vs. G-CSF/ATG-based protocol	0.71 (0.46–1.10)	0.13	/	/
PTCy+ATG^{low} based vs. G-CSF/ATG-based	0.60 (0.38–0.95)	**0.030**	/	/

aGvHD, acute graft-versus-host disease; ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; ATG, antithymocyte globulin; cGvHD, chronic graft-versus-host disease; CI, confidence interval; DRI, disease risk index; G-CSF, granulocyte colony-stimulating factor; HCT-CI, hematopoietic cell transplantation-comorbidity index; HR, hazard ratio; MDS, myelodysplastic syndromes; PTCy, posttransplantation cyclophosphamide.