Received: 11 April 2025 | Accepted: 22 August 2025

DOI: 10.1111/bjh.70133

BJHaem
BRITISH JOURNAL OF HAEMATOLOGY

ORIGINAL PAPER

Transplantation & Cellular Therapy

Clinical outcomes of modified post-transplantation cyclophosphamide versus granulocyte colony-stimulating factor/anti-thymocyte globulin-based protocol in alternative donor transplantation for severe aplastic anaemia

Liangliang Wu[1,2] | Ming Zhou[1,2] | Xiaowei Chen[1,2] | Wenjian Mo[1,2] | Ruiqing Zhou[1,2] | Yumiao Li[1,2] | Caixia Wang[1,2] | Shilin Xu[1,2] | Fangfang Yang[1,2] | Yuling Zhang[1,2] | Xiaoqing He[1,2] | Xinxin Li[1,2] | Shunqing Wang[1,2] | Yuping Zhang[1,2]

[1]Department of Hematology, Institute of Blood Transfusion and Hematology, Guangzhou First People's Hospital, Guangzhou Medical University, Guangzhou, China

[2]Department of Hematology, Guangzhou First People's Hospital, South China University of Technology, Guangzhou, China

Correspondence
Yuping Zhang and Shunqing Wang, Department of Hematology, Guangzhou First People's Hospital, Panfu Road, Guangzhou 510180, Guangdong, China.
Email: eyzhangyuping@scut.edu.cn and eywangshq@scut.edu.cn

Funding information
National Key R&D program of China, Grant/Award Number: 2023YFA1800100; 2019 Annual Research Project of The China Marrow Donor Program, Grant/Award Number: CMDP201902; Guangzhou General Science and Technology Project of Health and Family Planning, Grant/Award Number: 20241A011012; Innovative Clinical Technique of Guangzhou, Grant/Award Number: 2019GX04 and 2023C-GX01; Guangzhou Municipal Science and Technology Project, Grant/Award Number: 2024A03J1021

Summary
Post-transplantation cyclophosphamide (PTCy) and granulocyte colony-stimulating factor/anti-thymocyte globulin (G-CSF/ATG) are established protocols for alternative donor haematopoietic stem cell transplantation (AD-HSCT) in severe aplastic anaemia (SAA). A modified PTCy (mPTCy) regimen, featuring increased ATG dosing (2.0 mg/kg/day, days −5 to −3) and reduced cyclophosphamide (40 mg/kg/day, days +3 and +4), showed promising outcomes in a prospective study but lacks direct comparison with G-CSF/ATG. This post hoc comparative analysis utilized data from our prospective mPTCy cohort (ChiCTR2000038297, $n = 101$, plus a 1-year protocol-consistent enrolment extension, $n = 56$) and a retrospective historical G-CSF/ATG cohort ($n = 140$) to compare outcomes in AD-HSCT. Both protocols showed similar incidences of engraftment, graft failure and overall survival. Multivariate analysis confirmed reduced risks of 100-day grade II–IV acute graft-versus-host disease (GVHD) (hazard ratio [HR] 0.43, 95% confidence interval [CI] 0.26–0.71, $p < 0.001$) and 2-year chronic GVHD (HR 0.33, 95% CI 0.17–0.65, $p = 0.001$), and improved 2-year GVHD, relapse/rejection-free survival (GRFS; HR 0.51, 95% CI 0.32–0.83, $p = 0.007$) with mPTCy versus G-CSF/ATG. Subgroup analysis revealed superior outcomes with mPTCy in haploidentical-HSCT, while outcomes were comparable between protocols in unrelated donor HSCT. These findings suggest mPTCy superiority over G-CSF/ATG in SAA patients undergoing AD-HSCT, especially haploidentical-HSCT, by reducing GVHD and improving GRFS.

KEYWORDS
AD-HSCT, G-CSF/ATG, mPTCy, SAA

INTRODUCTION

Allogeneic haematopoietic stem cell transplantation (allo-HSCT) from an human leukocyte antigen (HLA)-matched sibling donor (MSD) is a standard treatment for severe aplastic anaemia (SAA).[1,2] For patients lacking an MSD, alternative donor (AD) HSCT strategies, including haploidentical donor (HID) and unrelated donor (URD) HSCT (HLA 10/10 matched [MUD] and HLA 9/10 mismatched [MMUD]), have advanced and are widely used.[3–9]

Liangliang Wu, Ming Zhou and Xiaowei Chen contributed equally to this study.

Post-transplantation cyclophosphamide (PTCy) and granulocyte colony-stimulating factor (G-CSF)/anti-thymocyte globulin (ATG) (G-CSF/ATG)-based approaches are the major protocols used for AD-HSCT.[6,9–14] Building on the classical Baltimore PTCy protocol,[9,12,13,15,16] several adapted protocols have achieved promising outcomes by altering stem cell sources with combined mobilized bone marrow (BM) and peripheral blood stem cells (PBSCs),[17] adopting ATG- and total body irradiation (TBI)-free regimen,[18] and reducing Cy dosage to 14.5 mg/kg on days +3 and +4.[19] At our institute, we prospectively implemented a modified PTCy (mPTCy) protocol for AD-HSCT (ChiCTR2000038297), featuring an increased ATG dose (from 4.5 to 6.0 mg/kg) with timing shifted from days −9 to −7 to days −5 to −3, and reduced Cy doses (50 to 40 mg/day on days +3 and +4), and graft optimization with combined mobilized BM and PBSCs for HID-HSCT and mobilized PBSCs for URD-HSCT, also achieving excellent clinical outcomes.[3,4]

Two published studies have compared the clinical outcomes of PTCy and G-CSF/ATG-based protocols, demonstrating similar cumulative incidences (CuI) of acute and chronic graft-versus-host disease (GVHD) and overall survival (OS).[20,21] However, the relatively small number of SAA patients receiving HID-HSCT in these studies constrained the strength of the conclusions. Additionally, the comparison of these two protocols in URD-HSCT for SAA remains unexplored. Given the promising results of the prospective mPTCy study for AD-HSCT observed at our centre,[3,4] we expanded our study by 1 year and conducted a post hoc comparative analysis combining prospective mPTCy and retrospective G-CSF/ATG data to identify a better approach for SAA AD-HSCT.

METHODS

Patients

All patients were diagnosed with SAA based on published criteria.[22,23] Eligibility required the absence of an available MSD, voluntary donation and physical fitness from HID or URD. Patients with hereditary BM failure and SAA patients complicated with active paroxysmal nocturnal haemoglobinuria—defined by ongoing haemolysis and/or thrombotic complications—were excluded. The prospective mPTCy study, registered at the Chinese Clinical Trial Registry (ChiCTR2000038297), included 101 patients (71 HID-HSCT and 30 URD-HSCT) enrolled from July 2019 to June 2022.[3,4] An additional 56 patients were enrolled (July 2022 to June 2023) as a protocol-consistent extension of the mPTCy study. The historical control cohort included retrospectively enrolled patients who received G-CSF/ATG-based AD-HSCT between August 2012 and September 2021. The last follow-up for the survivors was on 30 June 2024. Written informed consent was obtained from all patients or their legal guardians in accordance with the Declaration of Helsinki. The study was approved by the Institutional Review Board of Guangzhou First People's Hospital (B-2019-004-01).

Additional definitions, transplantation procedure, HLA typing and stem cell harvesting and assessment of engraftment and supportive care were listed in the Supporting Information Methods.

Study end-points

The primary end-point was the 100-day CuI of grade II–IV acute GVHD (aGVHD) and the 2-year CuI of chronic GVHD (cGVHD). Secondary end-points included 28-day CuI of neutrophil engraftment, 100-day CuI of platelet engraftment, 2-year CuIs of Cytomegalovirus (CMV) and Epstein–Barr virus (EBV) infection, post-transplant lymphoproliferative disorder (PTLD) and graft failure (GF), 2-year OS and 2-year GVHD, relapse/rejection-free survival (GRFS). OS was calculated from transplantation to death or the last follow-up. GRFS events included primary and secondary GF, relapse, grade III–IV aGVHD, moderate/severe cGVHD and death.

Statistical analysis

Continuous variables were summarized as medians (interquartile range, IQR) or mean ± standard error and categorical variables as frequencies (percentages). Group comparisons used the Student's *t*-test or Mann–Whitney *U*-test for continuous variables and the chi-squared or Fisher's exact test for categorical variables. CuIs of engraftment, GF, aGVHD, cGVHD, CMV and EBV infection and PTLD were estimated using competing risk analysis based on Gray's test, with death from any cause as a competing event. Survival probabilities were calculated using the Kaplan–Meier method and compared with the log-rank test.

Univariable and multivariable Cox regression models were used to estimate hazard ratios (HRs) for GRFS in the overall AD-HSCT cohort and the HID-HSCT subgroup. Covariates included age, sex, diagnosis, time from diagnosis to transplantation, transplantation protocol, prior treatment, graft source, mononuclear cell count, $CD34^+$ cell count, donor–recipient ABO compatibility and donor–recipient sex match, with type of transplantation added for the overall AD-HSCT cohort and donor–recipient relation for the HID-HSCT subgroup. Multivariable Fine–Gray subdistribution hazard models, incorporating the same covariates as in the GRFS analysis and including aGVHD as an additional covariate for the cGVHD model, were used to assess risks of 100-day aGVHD and 2-year cGVHD, accounting for death as a competing risk. Four patients (three HID and one URD in the G-CSF/ATG group) missing $CD34^+$ cell count data were excluded from analyses. Variables with $p < 0.1$ in univariable Cox regression and Fine–Gray analysis were included in the multivariable models. EBV and CMV viraemia

risks were assessed using Fine–Gray subdistribution hazard models, adjusted for rituximab and letermovir prophylaxis effects on CuI respectively.[24,25] All analyses were conducted using R version 4.1.3 (http://www.r-project.org). Statistical significance was defined as $p < 0.05$.

RESULTS

Patient characteristics

A total of 297 AD-HSCT patients were included: 157 received mPTCy and 140 received G-CSF/ATG (Figure 1). Baseline characteristics were comparable between groups except for a shorter median interval from diagnosis to transplant in the mPTCy group (4 months, IQR 2–14 vs. 7 months, IQR 2–60, $p = 0.005$) and lower median infused cell doses: mononuclear cells (9.59×10^8/kg, IQR 9.03–10.40 vs. 10.9×10^8/kg, IQR 9.85–12.10, $p < 0.001$) and $CD34^+$ cells (3.44×10^6/kg, IQR 2.42–4.83 vs. 4.49×10^6/kg, IQR 2.90–6.16, $p = 0.002$). Additional details are provided in Table 1.

Engraftment

Compared to the G-CSF/ATG cohort, patients receiving mPTCy experienced a significantly prolonged median time to neutrophil engraftment (13 days, IQR 13–15 vs. 11 days, IQR 10–12, $p < 0.001$), whereas platelet engraftment time was comparable (11.5 days, IQR 10–14 vs. 11 days, IQR 10–15, $p = 0.179$) (Table 1). The CuI of 28-day neutrophil engraftment was slightly higher in the mPTCy group (97.5% ± 1.3% vs. 96.4% ± 1.6%, $p < 0.001$), with no significant differences in the CuI of 100-day platelet engraftment and 2-year GF (Figure 2A–C).

Subgroup analyses of HID-HSCT and URD-HSCT cohorts also showed consistent patterns, showing delayed neutrophil engraftment in the mPTCy group (median, HID:

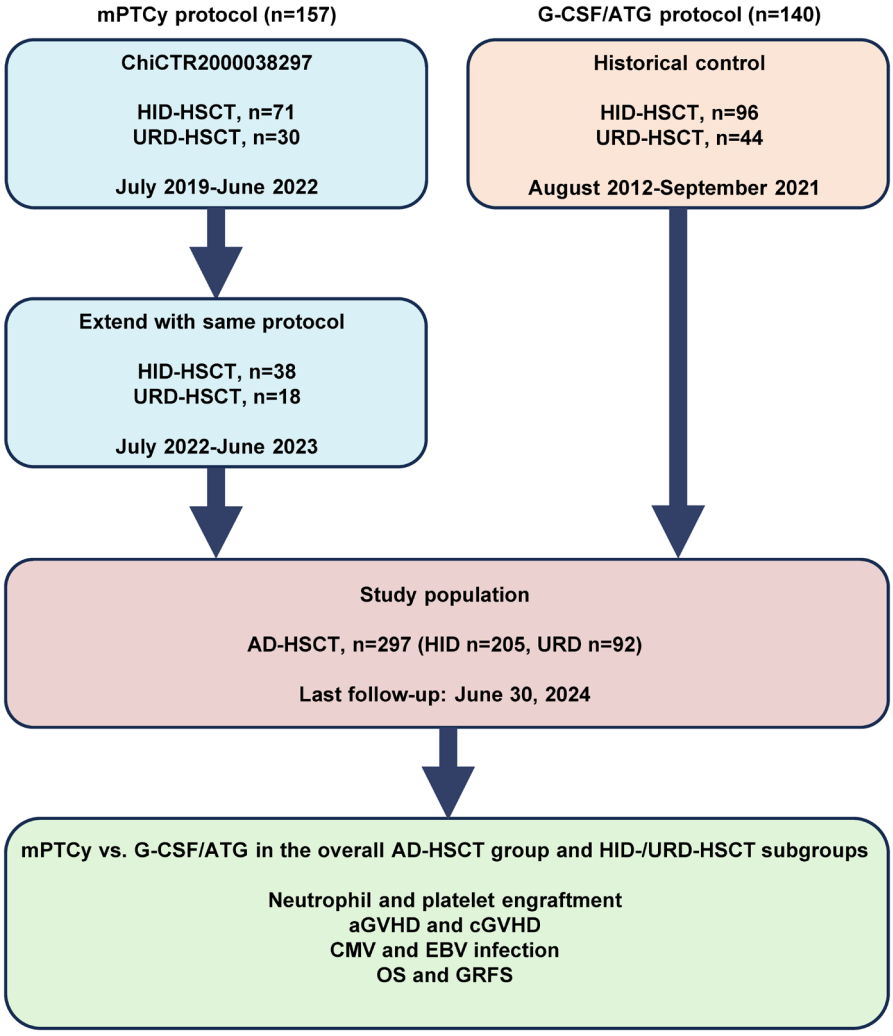

FIGURE 1 Schematic of patients included in present study. AD-HSCT, alternative donor haematopoietic stem cell transplantation; aGVHD, acute graft-versus-host disease; cGVHD, chronic graft-versus-host disease; CMV, cytomegalovirus; EBV, Epstein–Barr virus; G-CSF/ATG, granulocyte colony-stimulating factor/anti-thymocyte globulin; GRFS, relapse/rejection-free survival; HID, haploidentical donor; mPTCy, modified post-transplantation cyclophosphamide; OS, overall survival; URD, unrelated donor. [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Patient characteristics in transplantation.

Characteristics	AD-HSCT			HID-HSCT			URD-HSCT		
	G-CSF/ATG (*n* = 140)	mPTCy (*n* = 157)	*p*	G-CSF/ATG (*n* = 96)	mPTCy (*n* = 109)	*p*	G-CSF/ATG (*n* = 44)	mPTCy (*n* = 48)	*p*
Age at transplant, years, median (IQR)	29.0 (21.0, 38.0)	27.0 (18.0, 36.0)	0.082	26.5 (20.0, 34.2)	25.0 (17.0, 36.0)	0.717	33.0 (29.0, 43.0)	29.5 (20.2, 37.0)	0.008
Gender, *n* (%)			0.738			0.407			0.696
Female	57 (40.7)	68 (43.3)		35 (36.5)	47 (43.1)		22 (50.0)	21 (43.8)	
Male	83 (59.3)	89 (56.7)		61 (63.5)	62 (56.9)		22 (50.0)	27 (56.3)	
Interval diagnosis to transplant, months, median (IQR)	7 (2, 60)	4 (2, 14)	0.005	5 (2.0, 43.5)	2.0 (1.5, 7.0)	0.008	11.5 (4, 87)	9 (5, 56.8)	0.181
Diagnosis, *n* (%)			1.000			0.756			0.436
NSAA	8 (5.7)	9 (5.7)		2 (2.1)	3 (2.8)		6 (13.6)	6 (12.5)	
SAA	64 (45.7)	72 (45.9)		39 (40.6)	39 (35.8)		25 (56.8)	33 (68.8)	
VSAA	68 (48.6)	76 (48.4)		55 (57.3)	67 (61.5)		13 (29.5)	9 (18.8)	
Prior treatment, *n* (%)			0.279			1.000			0.117
None/CSA ± TPO-RA	120 (85.7)	142 (90.4)		87 (90.6)	99 (90.8)		33 (75.0)	43 (89.6)	
ATG-based IST	20 (14.3)	15 (9.6)		9 (9.4)	10 (9.2)		11 (25.0)	5 (10.4)	
Graft source, *n* (%)			0.757			0.526			-
BM + PBSC	93 (66.4)	108 (68.8)		93 (96.9)	108 (99.1)		-	-	
PBSC	47 (33.6)	49 (31.2)		3 (3.1)	1 (0.9)		44 (100)	48 (100)	
Neutrophil engraftment time, days, median (IQR)	11 (10, 12)	13 (13, 15)	<0.001	11 (10, 12)	13 (13, 15)	<0.001	11 (10, 14)	13 (13, 14.5)	0.032
Platelet engraftment time, days, median (IQR)	11 (10, 15)	11.5 (10, 14)	0.179	12 (10, 14.5)	11 (10, 14)	0.369	11 (10, 14.8)	12 (10.2, 14)	0.318
Donor/patient gender, *n* (%)			0.444			0.286			0.791
Female/female	12 (8.6)	14 (8.9)		9 (9.4)	9 (8.3)		3 (6.8)	5 (10.4)	
Male/male	67 (47.9)	62 (39.5)		47 (49.0)	40 (36.7)		20 (45.5)	22 (45.8)	
Male/female	44 (31.4)	54 (34.4)		26 (27.1)	38 (34.9)		18 (40.9)	16 (33.3)	
Female/male	17 (12.1)	27 (17.2)		14 (14.6)	22 (20.2)		3 (6.8)	5 (10.4)	
ABO match, *n* (%)			0.263			0.786			0.071
Matched	72 (51.4)	84 (53.5)		57 (59.4)	64 (58.7)		15 (34.1)	20 (41.7)	
Minor mismatched	32 (22.9)	34 (21.7)		21 (21.9)	20 (18.3)		11 (25.0)	14 (29.2)	
Major mismatched	28 (20.0)	22 (14.0)		13 (13.5)	16 (14.7)		15 (34.1)	6 (12.5)	
Different	8 (5.7)	17 (10.8)		5 (5.2)	9 (8.3)		3 (6.8)	8 (16.7)	
Protocol, *n* (%)			<0.001			<0.001			<0.001
G-CSF/ATG	140 (100)	0 (0)		96 (100)	0 (0)		44 (100)	0 (0)	
mPTCY-BU	0 (0)	57 (36.3)		0 (0)	33 (30.3)		0 (0)	24 (50.0)	
mPTCY-TBI	0 (0)	100 (63.7)		0 (0)	76 (69.7)		0 (0)	24 (50.0)	

TABLE 1 (Continued)

Characteristics	AD-HSCT			HID-HSCT			URD-HSCT		
	G-CSF/ATG ($n=140$)	mPTCy ($n=157$)	p	G-CSF/ATG ($n=96$)	mPTCy ($n=109$)	p	G-CSF/ATG ($n=44$)	mPTCy ($n=48$)	p
MNC count, $\times10^8$/kg, median (IQR)	10.9 (9.85, 12.10)	9.59 (9.03, 10.40)	<0.001	11.30 (10.20, 12.30)	9.56 (9.04, 10.30)	<0.001	10.30 (8.67, 11.5)	9.62 (8.76, 10.4)	0.144
$CD34^+$ cell count, $\times10^6$/kg, median (IQR)	4.49 (2.90, 6.16)	3.44 (2.42, 4.83)	0.002	4.47 (2.96, 5.84)	3.22 (2.23, 4.38)	<0.001	4.59 (2.45, 7.16)	4.24 (2.98, 6.12)	0.399
Donor/patient relation, *n* (%)			0.008			0.003			-
Sibling	41 (29.3)	63 (40.1)		41 (42.7)	63 (57.8)		-	-	
Child/parent	20 (14.3)	6 (3.8)		20 (20.8)	6 (5.5)		-	-	
Parent/child	35 (25.0)	40 (25.5)		35 (36.5)	40 (36.7)		-	-	
URD	44 (31.4)	48 (30.6)		-	-		-	-	
Type of transplantation			0.245						0.144
HID	96 (68.6)	109 (69.4)		-	-		-	-	
MUD	26 (18.6)	20 (12.7)		-	-		26 (59.1)	20 (41.7)	
MMUD	18 (12.9)	28 (17.8)		-	-		18 (40.9)	28 (58.3)	
Follow-up time for surviving patients, days, median (IQR)	2511 (2148, 3042)	866 (639, 1259)	<0.001	2768 (2290, 3266)	951 (646, 1370)	<0.001	2194 (1712, 2417)	795 (621, 1143)	<0.001
Cause of death, *n* (%)[a]			-			-			-
GVHD	4 (2.9)	0 (0)		3 (3.1)	0 (0)		1 (2.3)	0 (0)	
Haemorrhage	3 (2.1)	0 (0)		3 (3.1)	0 (0)		0 (0)	0 (0)	
Infection	11 (7.9)	11 (7.0)		10 (10.4)	8 (7.3)		1 (2.3)	3 (6.3)	
PTLD	1 (0.7)	0 (0)		1 (1.0)	0 (0)		0 (0)	0 (0)	
Suicide	1 (0.7)	0 (0)		1 (1.0)	0 (0)		0 (0)	0 (0)	
Clonal evolution	0 (0)	1 (0.6)		0 (0)	1 (0.9)		0 (0)	0 (0)	
Organ failure	0 (0)	2 (1.3)		0 (0)	2 (1.8)		0 (0)	0 (0)	
Primary GF	0 (0)	3 (1.9)		0 (0)	3 (2.8)		0 (0)	0 (0)	
Secondary GF	3 (2.1)	0 (0)		3 (3.1)	0 (0)		0 (0)	0 (0)	
Withdrew	0 (0)	2 (1.3)		0 (0)	2 (1.8)		0 (0)	0 (0)	

Abbreviations: AD-HSCT, alternative donor haematopoietic stem cell transplantation; BM, bone marrow; CSA, ciclosporin; G-CSF/ATG, granulocyte colony-stimulating factor/anti-thymocyte globulin; GF, graft failure; GRFS, relapse/rejection-free survival; GVHD, graft-versus-host disease; HID, haploidentical donor; IQR, interquartile range; IST, immunosuppressive therapy; MNC, mononuclear cell count; mPTCy, modified post-transplantation cyclophosphamide; MUD, HLA 10/10 matched unrelated donor; MMUD, HLA 9/10 mismatched unrelated donor; NSAA, non-severe aplastic anaemia; PBSC, peripheral blood stem cell; PTCy, post-transplantation cyclophosphamide; PTLD, post-transplant lymphoproliferative disorder; SAA, severe aplastic anaemia; TBI, total body irradiation; TPO-RA, thrombopoietin receptor agonists; URD, unrelated donor; VSAA, very severe aplastic anaemia.

[a]List the detailed causes of death without performing a statistical comparison between groups.

13 days, IQR 13–15 vs. 11 days, IQR 10–12, $p < 0.001$; URD: 13 days, IQR 13–14.5 vs. 11 days, IQR 10–14, $p = 0.032$) but similar platelet engraftment time (Table 1). The CuI of 28-day neutrophil engraftment was slightly higher in mPTCy within HID-HSCT (97.2% ± 1.7% vs. 95.8% ± 2.2%, $p = 0.002$), but similar in URD-HSCT. CuIs for 100-day platelet engraftment and 2-year GF remained similar between mPTCy and G-CSF/ATG protocols across subgroups (Figure 2D–I).

GVHD

The mPTCy group demonstrated significantly lower 100-day CuI of grade II–IV aGVHD (16.6% ± 3.0% vs. 31.6% ± 4.0%; $p = 0.002$) and reduced 2-year CuIs of both cGVHD (8.1% ± 2.2% vs. 25.0% ± 3.8%; $p = 0.001$) and moderate-to-severe cGVHD (6.1% ± 2.0% vs. 18.2% ± 3.4%; $p = 0.002$) (Figure 3A,C,D). The 100-day CuI of grade III–IV aGVHD was also lower (1.9% ± 1.1% vs. 5.7% ± 2.0%), but not statistically significant ($p = 0.082$) (Figure 3B).

In the HID subgroup, the mPTCy group showed significantly lower 100-day CuI of grade II–IV aGVHD (18.3% ± 3.7% vs. 37.9% ± 5.1%; $p = 0.001$) and reduced 2-year CuIs of both cGVHD (8.8% ± 2.8% vs. 27.0% ± 4.7%; $p < 0.001$) and moderate-to-severe cGVHD (5.9% ± 2.3% vs. 16.9% ± 4.0%; $p = 0.015$), although the 100-day grade III–IV aGVHD remained a non-significant difference (1.8% ± 1.3% vs. 7.3% ± 2.7%; $p = 0.057$) (Figure 3E–H). Conversely, URD-HSCT recipients showed comparable 100-day CuI of grade II–IV (12.5% ± 4.8% vs. 18.2% ± 5.9%, $p = 0.473$) and grade

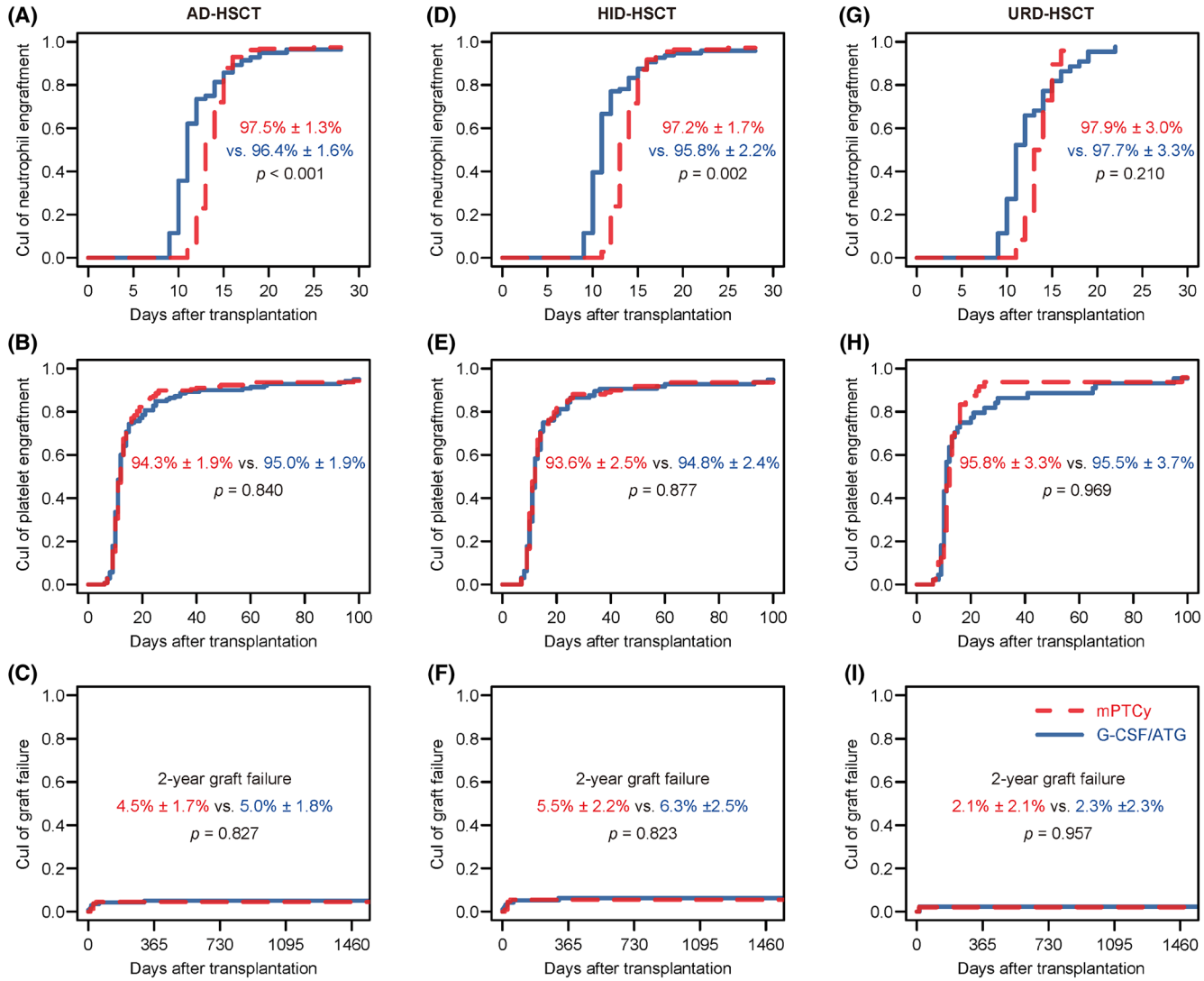

FIGURE 2 Comparison of engraftment and graft failure between mPTCy and G-CSF/ATG protocols. (A) 28-day neutrophil engraftment in AD-HSCT. (B) 100-day platelet engraftment in AD-HSCT. (C) 2-year GF in AD-HSCT. (D) 28-day neutrophil engraftment in HID-HSCT. (E) 100-day platelet engraftment in HID-HSCT. (F) 2-year GF in HID-HSCT. (G) 28-day neutrophil engraftment in URD-HSCT. (H) 100-day platelet engraftment in URD-HSCT. (I) 2-year GF in URD-HSCT. The CuI of neutrophil and platelet engraftment and GF were estimated using competing risk analysis based on Gray's test with death from any cause as a competing event. Statistical significance was defined as $p < 0.05$. AD-HSCT, alternative donor haematopoietic stem cell transplantation; G-CSF/ATG, granulocyte colony-stimulating factor/anti-thymocyte globulin; HID, haploidentical donor; HSCT, haematopoietic stem cell transplantation; mPTCy, modified post-transplantation cyclophosphamide; URD, unrelated donor. [Colour figure can be viewed at wileyonlinelibrary.com]

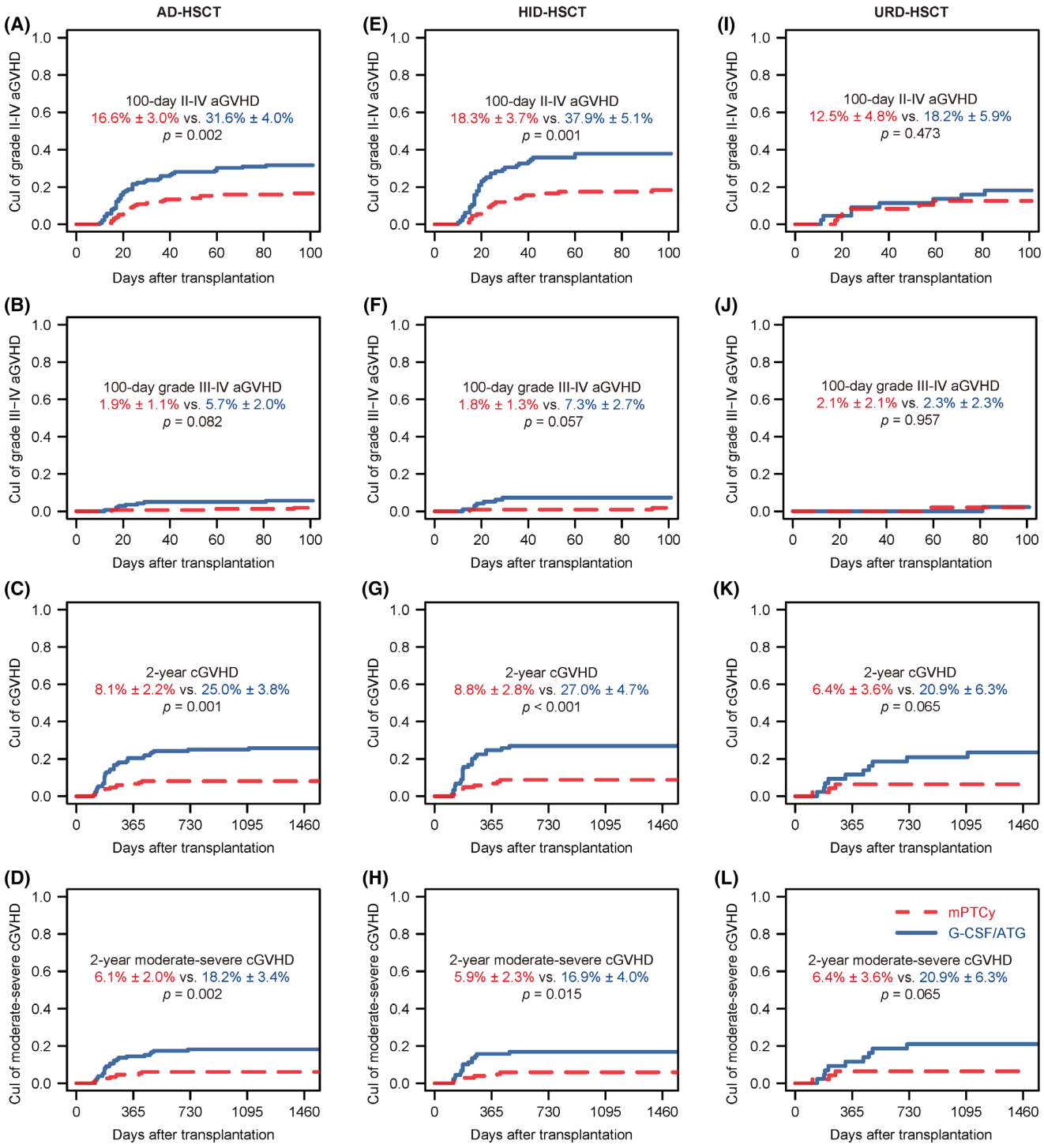

FIGURE 3 Comparison of aGVHD and cGVHD between mPTCy and G-CSF/ATG protocols. (A) 100-day grade II–IV aGVHD in AD-HSCT. (B) 100-day grade III–IV aGVHD in AD-HSCT. (C) 2-year cGVHD in AD-HSCT. (D) 2-year moderate–severe cGVHD in AD-HSCT. (E) 100-day grade II–IV aGVHD in HID-HSCT. (F) 100-day grade III–IV aGVHD in HID-HSCT. (G) 2-year cGVHD in HID-HSCT. (H) 2-year moderate–severe cGVHD in HID-HSCT. (I) 100-day grade II–IV aGVHD in URD-HSCT. (J) 100-day grade III–IV aGVHD in URD-HSCT. (K) 2-year cGVHD in URD-HSCT. (L) 2-year moderate–severe cGVHD in URD-HSCT. The CuI of aGVHD and cGVHD was estimated using competing risk analysis based on Gray's test with death from any cause as a competing event. Statistical significance was defined as $p < 0.05$. AD-HSCT, alternative donor haematopoietic stem cell transplantation; aGVHD, acute graft-versus-host disease; cGVHD, chronic graft-versus-host disease; G-CSF/ATG, granulocyte colony-stimulating factor/anti-thymocyte globulin; HID, haploidentical donor; mPTCy, modified post-transplantation cyclophosphamide; URD, unrelated donor. [Colour figure can be viewed at wileyonlinelibrary.com]

III–IV aGVHD (2.1% ± 2.1% vs. 2.3% ± 2.3%; $p = 0.957$) between the mPTCy and G-CSF/ATG groups (Figure 3I,J). Although the 2-year CuIs of cGVHD and moderate-to-severe cGVHD were lower in the mPTCy group (6.4% ± 3.6% vs. 20.9% ± 6.3% for both), the differences were not statistically significant ($p = 0.065$ for both) (Figure 3K,L).

Complications

The 2-year CuI of CMV viraemia was significantly lower in the mPTCy group than in the G-CSF/ATG group (66.5% ± 3.8% vs. 76.4% ± 3.6%; $p = 0.001$), while CMV disease incidence was comparable (10.2% ± 2.4% vs. 14.3% ± 3.0%; $p = 0.275$). Similarly, EBV viraemia incidence was reduced with mPTCy (3.2% ± 1.4% vs. 12.1% ± 2.8%; $p = 0.003$), whereas PTLD rates did not differ significantly (7.2% ± 2.1% vs. 4.3% ± 1.7%; $p = 0.318$). The CuIs of CMV and EBV viraemia were lower in HID-HSCT and URD-HST, except for CMV viraemia in URD-HSCT. Subgroup-specific CuIs are detailed in the Supporting Information Results.

Considering the prophylactic effects of letermovir and rituximab on CMV and EBV viraemia, we adjusted for their impact accordingly. After adjustment, HRs were 0.79 (95% CI 0.59–1.04; $p = 0.093$) for CMV viraemia and 0.65 (95% CI: 0.16–2.70; $p = 0.560$) for EBV viraemia in AD-HSCT with mPTCy. In the HID recipients, mPTCy reduced CMV viraemia risk (adjusted HR 0.64, 95% CI 0.46–0.88; $p = 0.007$) but not EBV viraemia (HR 1.28, 95% CI 0.15–10.82; $p = 0.82$). Among URD recipients, mPTCy showed no effect on CMV viraemia (adjusted HR 1.23, 95% CI 0.71–2.10; $p = 0.460$), and EBV analysis was precluded by absent events in the mPTCy group.

Survival outcome

During follow-up, there were 19 deaths in the mPTCy cohort compared to 23 in the G-CSF/ATG cohort, with infections being the primary cause in both groups (Table 1). Survivor follow-up was significantly shorter in the mPTCy group (median 866 days, IQR 639–1259 vs. 2511 days, IQR 2148–3042, $p < 0.001$). The 2-year OS did not differ between groups (87.4%, 95% CI 82.2–92.9 vs. 83.6%, 95% CI 77.7–89.9, $p = 0.336$, Figure 4A), whereas 2-year GRFS was significantly higher with mPTCy (82.6%, 95% CI 76.8–88.8 vs. 69.3%, 95% CI 62.1–77.4, $p = 0.007$; Figure 4B). In the HID-HSCT subgroup, 2-year OS remained comparable (84.7%, 95% CI 78.0–92.0 vs. 78.1%, 95% CI 70.3–86.9, $p = 0.213$, Figure 4C), but 2-year GRFS was superior with mPTCy (80.5%, 95% CI 73.3–88.4 vs. 65.6%, 95% CI 56.8–75.9, $p = 0.014$, Figure 4D). Conversely, the URD-HSCT subgroup showed no significant 2-year OS (93.8%, 95% CI 87.2–100 vs. 95.5%, 95% CI 89.5–100, $p = 0.689$, Figure 4E) and 2-year GRFS differences (87.5%, 95% CI 78.6–97.4 vs. 77.3%, 95% CI 65.8–90.7, $p = 0.247$, Figure 4F) between groups.

Multivariate analysis

Variables with $p < 0.1$ in univariate analysis (Fine–Gray for aGVHD/cGVHD; Cox for GRFS) are listed in Tables S1–S3. In multivariable Fine–Gray models, the mPTCy protocol significantly reduced the incidence of aGVHD by day 100 (HR 0.43, 95% CI 0.26–0.71, $p < 0.001$) and 2-year cGVHD (HR 0.33, 95% CI 0.17–0.65, $p = 0.001$) in the overall cohort (Table 2). Multivariable Cox regression confirmed proportional hazard (Schoenfeld residuals global $p = 0.520$) and demonstrated significantly improved 2-year GRFS with mPTCy (HR 0.51, 95% CI 0.32–0.83, $p = 0.007$, Table 3). This benefit extended to the HID-HSCT subgroup, where mPTCy reduced 100-day aGVHD (HR 0.44, 95% CI 0.25–0.77, $p = 0.005$), 2-year cGVHD (HR 0.39, 95% CI 0.18–0.86, $p = 0.019$) and improved 2-year GRFS (HR 0.51, 95% CI 0.29–0.88, $p = 0.015$) without proportional hazard violation (global $p = 0.710$) (Tables 2 and 3).

Furthermore, in both the overall AD-HSCT cohort and the HID-HSCT subgroup, patients without prior ATG-based immunosuppressive therapy (IST) who received mPTCy had a lower risk of 100-day grade II–IV aGVHD, reduced 2-year cGVHD and improved 2-year GRFS (see Supporting Information Methods and Results; Tables S4–S6; Figure S1). Conversely, among relapsed/refractory (R/R) patients, MUD and MMUD transplants showed comparable outcomes between the mPTCy and G-CSF/ATG groups for CuIs of 100-day aGVHD and 2-year cGVHD and 2-year GRFS (see Supporting Information Methods and Results; Tables S7 and S8; Figures S2 and S3).

Menstruation recovery

Although aGVHD, cGVHD and GRFS outcomes were comparable in URD recipients, we further analysed menstruation recovery in females aged 11–39 years. Given busulfan's established gonadotoxicity,[26,27] URD-HSCT recipients receiving mPTCy-Bu demonstrated poor 2-year CuI menstruation recovery (14.3% ± 14.3%). In contrast, mPTCy-TBI was associated with significantly higher 2-year menstruation recovery than G-CSF/ATG (66.7% ± 17.6% vs. 0%, $p < 0.001$), despite comparable baseline characteristics and no differences in aGVHD, cGVHD or GRFS (Table S9; Figure S4).

DISCUSSION

This study compared SAA patients receiving mPTCy versus G-CSF/ATG protocols for AD-HSCT. The mPTCy protocol showed lower CuI of aGVHD and cGVHD and improved GRFS. Subgroup analysis revealed that these benefits were notable in HID-HSCT, while outcomes were comparable in URD-HSCT. These findings suggest mPTCy is superior to G-CSF/ATG for SAA patients undergoing AD-HSCT, particularly in HID-HSCT.

Since SAA is a non-malignant disease that does not require a graft-versus-malignancy effect, minimizing GVHD is crucial, especially in AD-HSCT. In our mPTCy protocol, the use of combined mobilized PBSCs and BM grafts facilitated faster engraftment compared to prior PTCy regimens.[9,13,16] Given the association of PBSCs with increased GVHD risk,[28] we increased the ATG dose from 4.5 mg/kg to 6.0 mg/kg and shifted its administration from days −9 to −7

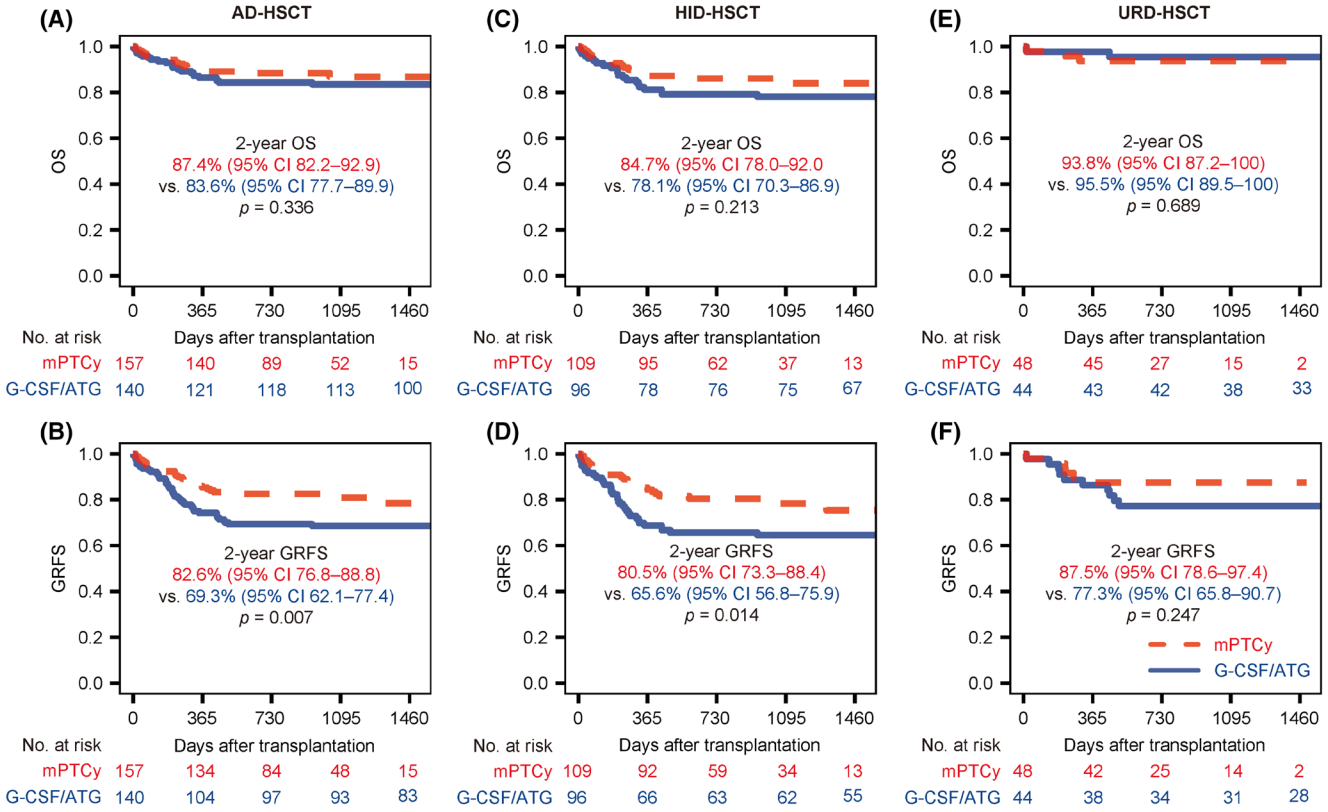

FIGURE 4 Comparison of survival outcomes between mPTCy and G-CSF/ATG protocols. (A) Two-year OS in AD-HSCT. (B) Two-year GRFS in AD-HSCT. (C) Two-year OS in HID-HSCT. (D) Two-year GRFS in HID-HSCT. (E) Two-year OS in URD-HSCT. (F) Two-year GRFS in URD-HSCT. OS and GRFS were calculated using the Kaplan–Meier method and compared with the log-rank test. Statistical significance was defined as $p < 0.05$. AD-HSCT, alternative donor haematopoietic stem cell transplantation; G-CSF/ATG, granulocyte colony-stimulating factor/anti-thymocyte globulin; GRFS, relapse/rejection-free survival; HID, haploidentical donor; mPTCy, modified post-transplantation cyclophosphamide; OS, overall survival; URD, unrelated donor. [Colour figure can be viewed at wileyonlinelibrary.com]

to days −5 to −3. Although two reports show a similar incidence of GVHD between G-CSF/ATG and PTCy-based protocols in SAA HID-HSCT,[20,21] our mPTCy protocol, with adjusted ATG dose and timing, may enhance donor T-cell depletion and mitigate GVHD risk.

Previous studies reported the incidence of aGVHD 30.3%–31.3%[8,29] and 33.7%–35.4%[30,31] for those without received ATG-based IST and R/R patients transplanted with G-CSF/ATG-based regimens respectively. Our data show a lower incidence of aGVHD at 16.9% and 13.3% for those without received ATG-based IST and R/R patients with mPTCy compared to the G-CSF/ATG protocol, which shows an incidence of 30.2% and 40.0%, respectively, consistent with previous multicentre studies.[8,29–31] The incidence of cGVHD with the mPTCy protocol was also lower than with the G-CSF/ATG protocol in both patients without prior ATG-based IST and R/R patients.[8,29–31] Although the difference was not statistically significant in R/R recipients, the small cohort size limited the analysis power. Multivariable analysis confirms the mPTCy protocol as protective against aGVHD and cGVHD for SAA in AD-HSCT overall and in the HID-HSCT subgroup. In URD-HSCT, G-CSF–primed PBSCs (the only graft source available through the Chinese Marrow Donor Program) may increase GVHD risk versus BM.[32] Yet, mPTCy showed comparable aGVHD and numerically lower cGVHD versus G-CSF/ATG, though nonsignificant (possibly due to small sample size), requiring further validation.

The OS and GRFS in SAA patients receiving HID or URD HSCT with PTCy protocol range from 78% to 97%[3,4,12,20,21,33–35] and 63% to 93%,[3,4,17,21,35] respectively. Our OS and GRFS results were comparable to those previously reported in patients without prior ATG-based IST,[12,13] and superior to historical data in R/R patients (OS 93.3% vs. 82.0%; GRFS: 78.8% vs. 63.0%)[35] respectively. Across the entire AD-HSCT cohort and within the HID-HSCT and URD-HSCT subgroups, no significant difference in 2-year OS was observed. However, similar to the GVHD outcomes, 2-year GRFS was better in the mPTCy group across the entire AD-HSCT and within HID-HSCT, but this improvement was not observed in URD-HSCT. The GRFS framework defines failure events to include not only mortality but also grade III-IV aGVHD and moderate–severe cGVHD. Hence, the lower incidence of aGVHD and cGVHD in the mPTCy-based protocol, compared to the G-CSF/ATG regimen, is crucial for improved GRFS outcomes.

The neutrophil engraftment is slower in the mPTCy group than in the G-CSF/ATG group in both HID and

TABLE 2 Multivariable analysis of risk factors for 100-day aGVHD and 2-year cGVHD cumulative incidence after transplantation.

	AD-HSCT		HID-HSCT	
Characteristics	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***
aGVHD				
Age, years				
≤40	-	-	1	-
>40	-	-	0.42 (0.15–1.21)	0.110
Protocol				
G-CSF/ATG	1	-	1	-
mPTCy	**0.43 (0.26–0.71)**	**<0.001**	**0.44 (0.25–0.77)**	**0.005**
Graft source				
BM + PBSC	1	-	-	-
PBSC	1.53 (0.26–8.93)	0.630	-	-
$CD34^+$ cell, $\times10^6$/kg	-	-	1.08 (0.95–1.24)	0.250
ABO match				
Matched	1	-	1	-
Minor mismatched	1.31 (0.76–2.24)	0.410	1.45 (0.81–2.60)	0.210
Major mismatched	0.46 (0.19–1.10)	0.085	0.37 (0.11–1.24)	0.110
Different	0.82 (0.29–2.25)	0.630	0.83 (0.26–2.59)	0.740
Type of transplantation				
HID	1	-	-	-
MUD	0.19 (0.03–1.40)	0.100	-	-
MMUD	0.48 (0.08–3.02)	0.440	-	-
cGVHD				
Age, years				
≤40	-	-	1	-
>40	-	-	0.21 (0.03–1.62)	0.130
Protocol				
G-CSF/ATG	1	-	1	-
mPTCy	**0.33 (0.17–0.65)**	**0.001**	**0.39 (0.18–0.86)**	**0.019**
Graft source				
BM + PBSC	-	-	1	-
PBSC	-	-	1.54 (0.65–3.67)	0.320
MNC, $\times10^8$/kg	-	-	1.05 (0.91–1.21)	0.530
$CD34^+$ cell, $\times10^6$/kg	-	-	1.12 (0.98–1.28)	0.093
ABO match				
Matched	1	-	1	-
Minor mismatched	1.81 (0.94–3.48)	0.075	1.88 (0.88–4.04)	0.110
Major mismatched	0.86 (0.32–2.29)	0.760	1.06 (0.30–3.69)	0.930
Different	1.57 (0.59–4.17)	0.370	1.12 (0.33–3.83)	0.860
History of aGVHD				
No	1	-	1	-
Yes	**2.54 (1.42–4.53)**	**0.002**	**2.01 (1.02–3.96)**	**0.043**

Abbreviations: AD-HSCT, alternative donor haematopoietic stem cell transplantation; aGVHD, acute graft-versus-host disease; BM, bone marrow; cGVHD, chronic graft-versus-host disease; G-CSF/ATG, granulocyte colony-stimulating factor/anti-thymocyte globulin; HID, haploidentical donor; HR, hazard ratio; MMUD, HLA 9/10 mismatched unrelated donor; MNC, mononuclear cell count; mPTCy, modified post-transplantation cyclophosphamide; MUD, HLA 10/10 matched unrelated donor; PBSC, peripheral blood stem cell.

Results with statistical significance are highlighted in bold.

URD-HSCT. However, the median time to neutrophil engraftment is faster in our protocol (13 days) than in the previous PTCy protocol (17 days),[13,34] likely due to PBSCs graft use. Nevertheless, no significant differences were observed in the CuI of platelet engraftment and GF between groups, whether in HID or URD-HSCT, or in the overall cohort.

TABLE 3 Multivariable analysis of risk factors for 2-year GRFS after transplantation.

	AD-HSCT		HID-HSCT	
Characteristics	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***
Gender				
Female	1	-	-	-
Male	1.42 (0.86–2.34)	0.174	-	-
Protocol				
G-CSF/ATG	1	-	1	-
mPTCy	**0.51 (0.32–0.83)**	**0.007**	**0.51 (0.29–0.88)**	**0.015**
Type of transplantation				
HID	1	-	-	-
MUD	0.43 (0.19–1.01)	0.053	-	-
MMUD	0.84 (0.43–1.66)	0.621	-	-

Abbreviations: AD-HSCT, alternative donor haematopoietic stem cell transplantation; G-CSF/ATG, granulocyte colony-stimulating factor/anti-thymocyte globulin; GRFS, relapse/rejection-free survival; HR, hazard ratio; HID, haploidentical donor; mPTCy, modified post-transplantation cyclophosphamide; MMUD, HLA 9/10 mismatched unrelated donor; MUD, HLA 10/10 matched unrelated donor.

Results with statistical significance are highlighted in bold.

Viral infections are common complications in allo-HSCT. After adjustment for prophylaxis, no significant differences in CMV/EBV viraemia were found in the overall AD-HSCT cohort, nor for EBV in HID-HSCT or CMV in URD-HSCT subgroups. However, mPTCy significantly reduced CMV risk in HID-HSCT (HR 0.64, 0.46–0.88, $p = 0.007$), contrasting with prior PTCy studies[20,21] and suggesting mPTCy may better preserve anti-CMV immunity and mitigate CMV reactivation risk in HID-HSCT.

Fertility, a crucial component of post-transplantation quality of life, warrants attention. Busulfan in the G-CSF/ATG protocol is notably gonadotoxic and may significantly increase the risk of infertility after transplantation.[26,27] Although the mPTCy protocol did not demonstrate a clear advantage in aGVHD, cGVHD or GRFS in URD-HSCT, analysis of menstruation recovery in females aged 11–39 revealed a significantly higher CuI with the mPTCy-TBI protocol compared to G-CSF/ATG, potentially attributed to the low TBI dose and application of gonadal shielding.[3] These findings suggest that the mPTCy-TBI protocol may provide superior fertility preservation in female patients.

Our study has several limitations. First, the integration of retrospective and prospective cohorts, along with the administration of the two treatment protocols during different time periods, may introduce potential biases. However, the overall outcomes in the G-CSF/ATG group align with recent literature (aGVHD 31.3%, cGVHD 29.3%, OS 87.1%) expectation in this context.[29] Second, the mPTCy group has a shorter follow-up, which was adequate for assessing aGVHD but limited the long-term outcomes such as cGVHD, OS and GRFS. Third, the heterogeneity of the mPTCy protocol, including mPTCy-BU and mPTCy-TBI, may bias GVHD and engraftment outcomes. Finally, the lack of significant benefit observed in aGVHD, cGVHD and GRFS with mPTCy in the URD-HSCT subgroup may be attributable to the limited sample size.

In conclusion, the mPTCy-based protocol is more effective than G-CSF/ATG for SAA patients undergoing AD-HSCT, particularly in HID-HSCT, with lower aGVHD, cGVHD incidence and improved GRFS. Larger cohort data and randomized trials are needed to further clarify clinical outcomes across AD-HSCT protocols.

AUTHOR CONTRIBUTIONS

Shunqing Wang and Yuping Zhang contributed to the conception and design of the research, patient management and manuscript revision. Liangliang Wu treated the patients, analysed the data and wrote the original manuscript. Ming Zhou and Xiaowei Chen contributed to patient management, data analysis and the drafting of the manuscript. Ruiqing Zhou, Yumiao Li, Caixia Wang, Shilin Xu, Fangfang Yang, Yuling Zhang, Xiaoqing He and Xinxin Li treated the patients and provided data. All authors approved the final version of the manuscript. The corresponding authors (Shunqing Wang and Yuping Zhang) had final responsibility for the decision to submit the paper for publication.

ACKNOWLEDGEMENTS

We would like to thank the patients and caregivers who were participating in this study.

FUNDING INFORMATION

This study was supported by grants from the National Key R&D Program of China (2023YFA1800100), the Innovative Clinical Technique of Guangzhou (2019GX04, 2023C-GX01), the 2019 Annual Research Project of the China Marrow Donor Program (No. CMDP201902), the Guangzhou Municipal Science and Technology Project (2024A03J1021) and the Guangzhou General Science and Technology Project of Health and Family Planning (20241A011012).

CONFLICT OF INTEREST STATEMENT

The authors declare no competing financial interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The study was approved by the Institutional Review Board of Guangzhou First People's Hospital (B-2019-004-01).

PATIENTS CONSENT STATEMENT

Written informed consent was obtained from all patients or their legal guardians in accordance with the Declaration of Helsinki.

CLINICAL TRIAL REGISTRATION

The mPTCy protocol was prospectively registered at the Chinese Clinical Trial Registry (ChiCTR2000038297).

ORCID

Liangliang Wu https://orcid.org/0000-0002-9178-8440
Shunqing Wang https://orcid.org/0000-0001-9418-4901
Yuping Zhang https://orcid.org/0000-0003-1055-2071

REFERENCES

1. Kulasekararaj A, Cavenagh J, Dokal I, Foukaneli T, Gandhi S, Garg M, et al. Guidelines for the diagnosis and management of adult aplastic anaemia: a British Society for Haematology guideline. Br J Haematol. 2024;204(3):784–804. https://doi.org/10.1111/bjh.19236
2. Iftikhar R, DeFilipp Z, DeZern AE, Pulsipher MA, Bejanyan N, Burroughs LM, et al. Allogeneic hematopoietic cell transplantation for the treatment of severe aplastic anemia: evidence-based guidelines from the American Society for Transplantation and Cellular Therapy. Transplant Cell Ther. 2024;30:1155–70. https://doi.org/10.1016/j.jtct.2024.09.017
3. Wu L, Zhou M, Li Y, Chen X, Mo W, Wang C, et al. Prospective study of a modified post-transplantation cyclophosphamide regimen for severe aplastic anemia patients with HLA-haploidentical transplantation. Transplant Cell Ther. 2023;29(7):463.e1–463.e7. https://doi.org/10.1016/j.jtct.2023.04.015
4. Chen X, Chen C, Zhou M, Wang C, Li Y, Zhou R, et al. Efficacy of a modified post-transplant cyclophosphamide regimen for unrelated donor hematopoietic stem cell transplantation in patients with severe aplastic anemia: a prospective study. Transplant Cell Ther. 2024;30(11):1099.e1–1099.e10. https://doi.org/10.1016/j.jtct.2024.08.016
5. Montoro J, Eikema DJ, Tuffnell J, Potter V, Kalwak K, Halkes CJM, et al. Alternative donor transplantation for severe aplastic anemia: a comparative study of the SAAWP EBMT. Blood. 2024;144(3):323–33. https://doi.org/10.1182/blood.2024024173
6. Zhang Y, Wu L, Mo W, Zhou M, Li Y, Chen X, et al. Comparable outcomes of first-line hematopoietic stem cell transplantation from unrelated and matched sibling donors in adult patients with aplastic anemia: a retrospective single-center study. Biol Blood Marrow Transplant. 2019;25(8):1567–75. https://doi.org/10.1016/j.bbmt.2019.03.020
7. Wu L, Liu L, Zhao X, Zhou M, Fu A, Zhang Y, et al. Unrelated donor hematopoietic stem cell transplantation compared to immunosuppressive therapy plus eltrombopag as first-line treatment for adults with severe aplastic anemia. Blood Cancer J. 2024;14(1):37. https://doi.org/10.1038/s41408-024-01021-x
8. Xu LP, Jin S, Wang SQ, Xia LH, Bai H, Gao SJ, et al. Upfront haploidentical transplant for acquired severe aplastic anemia: registry-based comparison with matched related transplant. J Hematol Oncol. 2017;10(1):25. https://doi.org/10.1186/s13045-017-0398-y
9. DeZern AE, Zahurak M, Symons H, Cooke K, Jones RJ, Brodsky RA. Alternative donor transplantation with high-dose post-transplantation cyclophosphamide for refractory severe aplastic anemia. Biol Blood Marrow Transplant. 2017;23(3):498–504. https://doi.org/10.1016/j.bbmt.2016.12.628
10. Lv M, Chang YJ, Huang XJ. Update of the "Beijing protocol" haploidentical hematopoietic stem cell transplantation. Bone Marrow Transplant. 2019;54(Suppl 2):703–7. https://doi.org/10.1038/s41409-019-0605-2
11. Devillier R, Dalle JH, Kulasekararaj A, Daveni M, Clement L, Chybicka A, et al. Unrelated alternative donor transplantation for severe acquired aplastic anemia: a study from the French Society of Bone Marrow Transplantation and Cell Therapies and the EBMT severe aplastic anemia working party. Haematologica. 2016;101(7):884–90. https://doi.org/10.3324/haematol.2015.138727
12. DeZern AE, Zahurak M, Symons HJ, Cooke KR, Huff CA, Jain T, et al. Alternative donor BMT with posttransplant cyclophosphamide as initial therapy for acquired severe aplastic anemia. Blood. 2023;141(25):3031–8. https://doi.org/10.1182/blood.2023020435
13. DeZern AE, Zahurak ML, Symons HJ, Cooke KR, Rosner GL, Gladstone DE, et al. Haploidentical BMT for severe aplastic anemia with intensive GVHD prophylaxis including posttransplant cyclophosphamide. Blood Adv. 2020;4(8):1770–9. https://doi.org/10.1182/bloodadvances.2020001729
14. Wu L, Chen X, Zhou M, Mo W, Zhou R, Li Y, et al. Comparative study of Bu/Cy/ATG and Flu/Cy/ATG conditioning regimens for unrelated donor hematopoietic stem cell transplantation in severe aplastic anemia. Transplant Cell Ther. 2025. https://doi.org/10.1016/j.jtct.2025.06.014
15. DeZern AE, Zahurak M, Jones RJ, Brodsky RA. Uniform conditioning regardless of donor in bone marrow transplantation for severe aplastic anemia. Haematologica. 2024;109(2):657–60. https://doi.org/10.3324/haematol.2023.284022
16. DeZern AE, Eapen M, Wu J, Talano JA, Solh M, Dávila Saldaña BJ, et al. Haploidentical bone marrow transplantation in patients with relapsed or refractory severe aplastic anaemia in the USA (BMT CTN 1502): a multicentre, single-arm, phase 2 trial. Lancet Haematol. 2022;9(9):e660–e669. https://doi.org/10.1016/s2352-3026(22)00206-x
17. Li Y, Wang N, Li L, Cao Y, Xu J, Wang J, et al. Haploidentical transplantation with modified post-transplantation cyclophosphamide for patients with primary aplastic anemia: a multicenter experience. Transplant Cell Ther. 2021;27(4):331.e1–331.e7. https://doi.org/10.1016/j.jtct.2021.01.018
18. Gong S, Chen C, Chen K, Yang R, Wang L, Yang K, et al. Alternative transplantation with post-transplantation cyclophosphamide in aplastic anemia: a retrospective report from the BMF-WG of Hunan Province, China. Transplant Cell Ther. 2023;29(1):48.e1–48.e7. https://doi.org/10.1016/j.jtct.2022.10.006
19. Ma X, Xu Z, Han T, Zhang Y, Han W, Fu H, et al. Low-dose post-transplant cyclophosphamide with G-CSF/ATG based haploidentical protocol provides favorable outcomes for SAA patients. Front Immunol. 2023;14:1173320. https://doi.org/10.3389/fimmu.2023.1173320
20. Xu L, Fu B, Wang W, Xu Y, Wu D, Wang S, et al. Haploidentical hematopoietic cell transplantation for severe acquired aplastic anemia: a case-control study of post-transplant cyclophosphamide included regimen vs. anti-thymocyte globulin & colony-stimulating factor-based regimen. Sci China Life Sci. 2020;63(6):940–2. https://doi.org/10.1007/s11427-019-9585-x
21. Li Y, Lu X, Wang N, Zhang X, Cao Y, Xiao Y, et al. Comparisons of modified post-transplantation cyclophosphamide and granulocyte Colony-stimulating factor/antithymocyte globulin regimens for haploidentical stem cell transplantation in patients with aplastic anemia.

Transplant Cell Ther. 2022;28(7):396.e1–396.e9. https://doi.org/10.1016/j.jtct.2022.04.021

22. Killick SB, Bown N, Cavenagh J, Dokal I, Foukaneli T, Hill A, et al. Guidelines for the diagnosis and management of adult aplastic anaemia. Br J Haematol. 2016;172(2):187–207. https://doi.org/10.1111/bjh.13853
23. Marsh JC, Ball SE, Cavenagh J, Darbyshire P, Dokal I, Gordon-Smith EC, et al. Guidelines for the diagnosis and management of aplastic anaemia. Br J Haematol. 2009;147(1):43–70. https://doi.org/10.1111/j.1365-2141.2009.07842.x
24. Patel C, Pasciolla M, Abramova R, Salerno D, Gomez-Arteaga A, Shore TB, et al. Pre-hematopoietic stem cell transplantation rituximab for Epstein-Barr virus and post-lymphoproliferative disorder prophylaxis in alemtuzumab recipients. Transplant Cell Ther. 2023;29(2):132.e1–132.e5. https://doi.org/10.1016/j.jtct.2022.10.023
25. Zhang Y, Chen X, Zhou M, Zhang Y, Chen C, Zhou R, et al. Letermovir effectively prevents cytomegalovirus infection in patients with aplastic anemia after hematopoietic stem cell transplantation: a real-world retrospective cohort study. Infect Dis Ther. 2024;13(2):345–59. https://doi.org/10.1007/s40121-024-00917-2
26. Sanders JE, Hawley J, Levy W, Gooley T, Buckner CD, Deeg HJ, et al. Pregnancies following high-dose cyclophosphamide with or without high-dose busulfan or total-body irradiation and bone marrow transplantation. Blood. 1996;87(7):3045–52.
27. Vidal A, Bora C, Jarisch A, Pape J, Weidlinger S, Karrer T, et al. Impact of haematopoietic stem cell transplantation for benign and malignant haematologic and non-haematologic disorders on fertility: a systematic review and meta-analysis. Bone Marrow Transplant. 2025;60(5):645–72. https://doi.org/10.1038/s41409-025-02520-6
28. Bashey A, Zhang MJ, McCurdy SR, St. Martin A, Argall T, Anasetti C, et al. Mobilized peripheral blood stem cells versus unstimulated bone marrow As a graft source for T-cell-replete haploidentical donor transplantation using post-transplant cyclophosphamide. J Clin Oncol. 2017;35(26):3002–9. https://doi.org/10.1200/jco.2017.72.8428
29. Xu ZL, Xu LP, Wu DP, Wang SQ, Zhang X, Xi R, et al. Comparable long-term outcomes between upfront haploidentical and identical sibling donor transplant in aplastic anemia: a national registry-based study. Haematologica. 2022;107(12):2918–27. https://doi.org/10.3324/haematol.2022.280758
30. Xu LP, Xu ZL, Wang SQ, Wu DP, Gao SJ, Yang JM, et al. Long-term follow-up of haploidentical transplantation in relapsed/refractory severe aplastic anemia: a multicenter prospective study. Sci Bull. 2022;67(9):963–70. https://doi.org/10.1016/j.scib.2022.01.024
31. Xu LP, Wang SQ, Wu DP, Wang JM, Gao SJ, Jiang M, et al. Haploidentical transplantation for acquired severe aplastic anaemia in a multicentre prospective study. Br J Haematol. 2016;175(2):265–74. https://doi.org/10.1111/bjh.14225
32. Alousi A, Wang T, Hemmer MT, Spellman SR, Arora M, Couriel DR, et al. Peripheral blood versus bone marrow from unrelated donors: bone marrow allografts have improved long-term overall and graft-versus-host disease-free, relapse-free survival. Biol Blood Marrow Transplant. 2019;25(2):270–8. https://doi.org/10.1016/j.bbmt.2018.09.004
33. Yang K, Gong S, Jiang T, Liang X, Hu J, Zhu P, et al. Haploidentical peripheral stem cell transplantation for young patients with severe aplastic anemia using post-transplantation cyclophosphamide and methotrexate. Transplant Cell Ther. 2021;27(5):429.e1–429.e7. https://doi.org/10.1016/j.jtct.2021.02.014
34. Arcuri LJ, Nabhan SK, Loth G, Atta EH, Oliveira M, Nichele S, et al. A case series of post-transplantation cyclophosphamide in unrelated donor hematopoietic cell transplantation for aplastic anemia. Biol Blood Marrow Transplant. 2020;26(9):e222–e226. https://doi.org/10.1016/j.bbmt.2020.05.023
35. Prata PH, Eikema DJ, Afansyev B, Bosman P, Smiers F, Diez-Martin JL, et al. Haploidentical transplantation and posttransplant cyclophosphamide for treating aplastic anemia patients: a report from the EBMT severe aplastic anemia working party. Bone Marrow Transplant. 2020;55(6):1050–8. https://doi.org/10.1038/s41409-019-0773-0

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Wu L, Zhou M, Chen X, Mo W, Zhou R, Li Y, et al. Clinical outcomes of modified post-transplantation cyclophosphamide versus granulocyte colony-stimulating factor/anti-thymocyte globulin-based protocol in alternative donor transplantation for severe aplastic anaemia. Br J Haematol. 2025;207(5):2059–2071. https://doi.org/10.1111/bjh.70133