Title

Long-term outcomes after haploidentical stem cell transplantation for hematologic malignancies.

Journal

Blood Advances, 8(12)

Authors

Saengboon, Supawee

Ciurea, Stefan

Popat, Uday

et al.

Publication Date

2024-06-25

DOI

10.1182/bloodadvances.2023010625

Peer reviewed

REGULAR ARTICLE

blood advances

Long-term outcomes after haploidentical stem cell transplantation for hematologic malignancies

Supawee Saengboon,[1,2] Stefan Ciurea,[3] Uday Popat,[1] Jeremy Ramdial,[1] Qaiser Bashir,[1] Amin Alousi,[1] Julianne Chen,[1] Gabriela Rondon,[1] Amanda Olson,[1] Jin Im,[1] Chitra Hosing,[1] Elizabeth Shpall,[1] Richard Champlin,[1] and Samer A. Srour[1]

[1]Department of Stem Cell Transplantation and Cellular Therapy, The University of Texas MD Anderson Cancer Center, Houston, TX; [2]Division of Hematology, Department of Internal Medicine, Faculty of Medicine, Thammasat University, Pathumthani, Thailand; and [3]Division of Hematology/Oncology, Department of Medicine, University of California, Irvine, CA

Key Point

- Haplo-SCT is associated with excellent long-term outcomes for patients who are relapse-free at 2 years after transplant.

The introduction of posttransplant cyclophosphamide (PTCy)–based graft-versus-host disease (GVHD) prophylaxis lead to significant improvements in haploidentical stem cell transplantation (haplo-SCT) outcomes over the past decade. We retrospectively assessed long-term outcomes of patients who had their first haplo-SCT between February 2009 and March 2019. Long-term survivors were defined as patients who were alive and disease-free at 2 years after transplant. Three hundred thirty-five patients with a median age of 48 years (range, 18-72) were identified. Of these, 142 patients were disease-free and alive at 2 years after transplant. The 4-year progression-free survival (PFS) and overall survival (OS) for all study patients were 42% and 47%, respectively. With a median follow-up of 52 months for the long-term survivor group, the 4-year PFS and OS were 94% and 96%, respectively. The 4-year cumulative incidence of relapse and non-relapse mortality (NRM) were 2.9% and 3.3%, respectively. Age ≥55 years was the only predictive factor in multivariate analysis for inferior PFS (hazard ratio [HR], 3.41; 95% confidence interval [CI], 1.21-9.60; $P = .020$) and OS (HR, 3.31; 95% CI, 1.08-10.18; $P = .037$). Thirteen patients (9%) died in the long-term survivor group, only 2 of whom died of relapsed disease. Secondary primary malignancy was the most frequent cause of NRM (n = 4), followed by infection (n = 2). For haplo-SCT with PTCy–based GVHD prophylaxis, our findings suggest an excellent long-term survival for patients who were disease-free and alive at 2 years after transplant. Late relapses were rare, and age was the only predictive factor for long-term outcomes.

Introduction

Allogeneic hematopoietic stem cell transplantation (allo-SCT) remains the only curative treatment intervention for a large proportion of patients with high-risk hematologic malignancies. Until late 2000s, successful transplants relied primarily on the availability of fully human leukocyte antigen (HLA)–matched donors, as patients with haploidentical stem cell transplantation (haplo-SCT) from first-degree mismatched related donors had poor outcomes.[1] The failure of haplo-SCT was mainly attributed to increased risk of graft-versus-host disease (GVHD), graft failure, and infections. The introduction of

Submitted 18 May 2023; accepted 20 February 2024; prepublished online on *Blood Advances* First Edition 23 March 2024. https://doi.org/10.1182/bloodadvances.2023010625.

Data are available on request from the corresponding author, Samer A. Srour (ssrour@mdanderson.org).

The full-text version of this article contains a data supplement.

posttransplant cyclophosphamide (PTCy) lead to remarkable improvements in unmanipulated haplo-SCT outcomes,[2-5] with significant reduction in GVHD, graft failure, and non-relapse mortality (NRM).

With the improved haplo-SCT outcomes, there has been a steady increase in the number of haplo-SCT recipients over the past decade. Hence, a larger proportion of patients now have access to allo-SCT, most of whom had otherwise in the past, limited alternative donor sources and a missed opportunity for cure. Despite the very encouraging early results, there remains limited data on the long-term outcomes for patients with high-risk hematologic malignancies who received haplo-SCT. We aimed from this study to assess the long-term outcomes of patients who underwent unmanipulated haplo-SCTs with PTCy–based GVHD prophylaxis.

Methods

Patients

In this retrospective study, we included all consecutive adult patients with high-risk hematologic malignancies who underwent their first haplo-SCT between February 2009 and March 2019. Disease eligibility included patients with acute myeloid leukemia, myelodysplastic syndrome (MDS), acute lymphoblastic leukemia, myeloproliferative neoplasms (MPNs), and patients with lymphoid malignancies. The study was approved by the institutional review board at The University of Texas MD Anderson Cancer Center.

Clinical endpoints

The primary end points included progression-free survival (PFS) and overall survival (OS) for the long-term survivors. Long-term survivors were defined as patients who were alive and disease-free at 2 years after transplant. Patients who relapsed/progressed or died without progression within 2 years of transplant were grouped under short-term disease-free survivors. OS was defined as the time from transplant to death from any cause. PFS was defined as the time from transplant to disease progression or death from any cause. Surviving patients were censored at the time of the last follow-up. Secondary end points included cumulative incidence of relapse (CIR), NRM and GVHD-free relapse-free survival (GRFS). NRM was defined as death without evidence of relapse or progression of malignancy. Disease relapse/progression was defined as any evidence of recurrence if they were in remission at time of transplant, otherwise defined as progression of malignancy if they were not in remission at time of transplant. GRFS was defined as the time from transplant to the first occurrence of any of the following events: grade 3-4 acute GVHD, extensive chronic GVHD, disease relapse or death from any cause.

Statistical analysis

The baseline patient-, disease-, and treatment-related characteristics were summarized using descriptive statistics. Median and range used for continuous measures and proportions and frequencies for categorical measures. For comparisons, the chi-square or Fisher exact test were used for categorical variables, and the Wilcoxon rank-sum test was used to compare continuous variables. Kaplan-Meier method was used to estimate time-to-event data including PFS and OS. Fine and Gray competing risk regression model was used to compute the cumulative incidence of progression/relapse and for NRM. The primary focus of this analysis was for patients who survived for at least 2 years after transplant without evidence of disease progression, and hence we chose the landmark cutoff point at 2 years for the long-term survivor group. Predictors of long-term survival were evaluated using Cox proportional hazards regression analysis. Variables with significant P value of $< .1$ in the univariate analysis were included in the final multivariate model. P values were 2-sided and significance level were set at $<.05$. The 95% confidence intervals (CIs) were provided for survival probabilities and/or cumulative incidences**.** Statistical analyses were performed using primarily STATA 16.0 (StataCorp, College Station, TX).

Results

Patient characteristics

Three hundred and thirty-five patients with a median age at transplantation of 48 years (range, 18-72) were identified during the study period. Of these, 142 patients were disease-free and alive at 2 years after transplant and were grouped under long-term survivors for the sake of this analysis. The median age for patients in the long-term survivor group was 45 years (range, 18-72). Table 1 summarizes patient, disease, and transplant characteristics for all study patients, long-term survivors, and short-term disease-free survivors. Overall, there were no notable differences in baseline characteristics between all study patients and the long-term survivors, but a higher proportion of patients with low/intermediate disease risk index (DRI) were noted in the long-term survivor group. A total of 183 patients were identified in the short-term disease-free survivor group: 88 had disease progression and 95 died within 2 years of transplant.

Compared with the long-term survivor group, these patients had significantly higher proportion of high/very high risk DRI (53% vs 27%; $P < .0001$), and were older (median age, 52 vs 45; $P = .086$) and with higher hematopoietic cell transplantation–specific comorbidity index of >3 (39% vs 30%; $P = .128$).

PFS and OS

With a median follow-up of 50 months (range, 5-133), the 4-year PFS and OS rates for all study patients were 42% and 47%, respectively (Figure 1A-B). For the long-term survivors, with a median follow-up of 52 months (range, 24-133), the median PFS and OS were not reached and the 4-year PFS and OS rates were 94% and 96%, respectively (Figure 1C-D).

Table 2 summarizes univariable analysis for several of the potential risk factors to predict transplant outcomes in the long-term survivor group (Table 2). In both univariable and multivariate analyses, only age ≥55 years was significantly associated with both inferior PFS (hazard ratio, 3.409; 95% CI, 1.211-9.600; $P = .020$) and OS (hazard ratio, 3.312; 95% CI, 1.078-10.180; $P = .037$). The 4-year and 8-year PFS for patients aged ≥55 years were 85% and 66%, respectively, compared with 97% and 88%, respectively, for those who were <55 years ($P = .0136$). Similarly, younger patients had better 4-year and 8-year OS of 97% and 90%, respectively, compared with 92% and 70%, respectively for patients aged ≥55 years ($P = .0268$) (Figure 2A-B).

Relapse

During the study period, a total of 92 (27%) relapsed, with a median time to relapse/progression for all study patients of

Table 1. Baseline patient, disease, and transplant characteristics for all study patients, and for long-term vs short-term survivors

	All study patients* (N=335)	Disease-free and alive at 2 years (N=142)	Progression and/or death at 2 years (N=183)	*P* value
Age at transplant, y				
Median (range)	48 (18-72)	45 (18-72)	52 (20-70)	.086
Age at transplant, n (%)				
<55 y	206 (61.49%)	95 (66.90%)	105 (57.38%)	.086
≥55 y	129 (38.51%)	47 (33.10%)	78 (42.62%)	
Gender, n (%)				
Male	195 (58.21%)	82 (57.75%)	105 (57.38%)	1.000
Female	140 (41.79%)	60 (42.25%)	78 (42.62%)	
Race, n (%)				
Asian	22 (6.71%)	9 (6.47%)	12 (6.70%)	
Black	69 (21.04%)	35 (25.18%)	32 (17.88%)	.374
Hispanic	72 (21.95%)	32 (23.02%)	39 (21.79%)	
White	165 (50.30%)	63 (45.32%)	96 (53.63%)	
Disease subtype, n (%)				
AML/MDS	195 (58.21%)	79 (55.63%)	112 (61.20%)	
ALL	55 (16.42%)	21 (14.79%)	32 (17.49%)	.115
MPNs	37 (11.04%)	22 (15.49%)	13 (7.10%)	
Lymphoid malignancies	48 (14.33%)	20 (14.08%)	26 (14.21%)	
Time from diagnosis to transplant, n (%)				
<6 mo	90 (26.87%)	38 (26.76%)	51 (27.87%)	.749
6-12 mo	80 (50.75%)	37 (26.06%)	41 (22.40%)	
>12 mo	165 (49.25%)	67 (47.18%)	91 (49.73%)	
Period of transplant, n (%)				
Transplant during 2009 to 2012	68 (20.30%)	29 (20.42%)	38 (20.77%)	
Transplant during 2013 to 2016	158 (47.16%)	69 (48.59%)	87 (47.54%)	.989
Transplant during 2017 to 2019	109 (32.54%)	44 (30.99%)	58 (31.69%)	
KPS at transplant, n (%)				
KPS 90-100	206 (68.21%)	92 (70.23%)	107 (66.05%)	.454
KPS < 90	96 (31.79%)	39 (29.77%)	55 (33.95%)	
DRI, n (%)				
Low/intermediate DRI	189 (59.06%)	99 (72.79%)	82 (47.13%)	<.0001
High/very high DRI	131 (40.94%)	37 (27.21%)	92 (52.87%)	
HCT-CI, n (%)				
HCT-CI ≤ 3	217 (64.78%)	99 (69.72%)	112 (61.20%)	.128
HCT-CI > 3	118 (35.22%)	43 (30.28%)	71 (38.80%)	
Stem cell source, n (%)				
Peripheral blood	53 (15.82%)	18 (12.68%)	32 (17.49%)	.279
Bone marrow	282 (84.18%)	124 (87.32%)	151 (82.51%)	
Conditioning regimen, n (%)				
Reduced intensity	297 (88.66%)	125 (88.03%)	164 (89.62%)	.723
Myeloablative	38 (11.34%)	17 (11.97%)	19 (10.38%)	
Patient-donor CMV, n (%)				
Seropositive-seropositive	185 (64.01%)	77 (65.81%)	102 (61.82%)	.531
Seropositive-seronegative	104 (35.99%)	40 (34.19%)	63 (38.18%)	

Totals may vary because of missing data.

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CMV, cytomegalovirus; DSA, donor-specific antibody; HCT-CI, hematopoietic cell transplantation–specific comorbidity index; KPS, Karnofsky performance scale.

*Ten patients had a follow-up time of <2 years and were disease-free and alive at time of last follow-up, and hence were excluded from the long-term survivor and the short-term disease-free survivor groups.

Table 1 (continued)

	All study patients* (N=335)	Disease-free and alive at 2 years (N=142)	Progression and/or death at 2 years (N=183)	*P* value
Donor age, n (%)				
<35 y	168 (50.15%)	67 (47.18%)	96 (52.46%)	.372
≥35 y	167 (49.85%)	75 (52.82%)	87 (47.54%)	
Donor/recipient gender, n (%)				
Male/male	125 (37.31%)	50 (35.21%)	69 (37.70%)	
Female/female	60 (17.91%)	29 (20.42%)	30 (16.39%)	.611
Male/female	80 (23.88%)	31 (21.83%)	48 (26.23%)	
Female/male	70 (20.90%)	32 (22.54%)	36 (19.67%)	
Donor/recipient relationship, n (%)				
Parent/child	36 (10.75%)	15 (10.56%)	20 (10.93%)	
Sibling/sibling	132 (39.40%)	62 (43.66%)	63 (34.43%)	.192
Child/parent	164 (48.96%)	65 (45.78%)	97 (53.00%)	
Other	3 (0.90%)	0	3 (1.64%)	
Anti-HLA antibody, n (%)				
No DSA	240 (71.64%)	105 (73.95%)	128 (69.95%)	
Anti HLA class I Ab	42 (12.54%)	16 (11.27%)	24 (13.11%)	.801
Anti HLA class II Ab	25 (7.46%)	9 (6.34%)	16 (8.74%)	
Anti HLA class I and II Ab	28 (8.36%)	12 (8.45%)	15 (8.20%)	
Acute GVHD grades 2-4, n (%)				
No	191 (57.01%)	90 (63.38%)	96 (52.46%)	.055
Yes	144 (42.99%)	52 (36.62%)	87 (47.54%)	
Chronic GVHD, n (%)				
No	290 (86.57%)	114 (80.28%)	167 (91.26%)	.005
Yes	45 (13.43%)	28 (19.72%)	16 (8.74%)	

Totals may vary because of missing data.

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CMV, cytomegalovirus; DSA, donor-specific antibody; HCT-CI, hematopoietic cell transplantation–specific comorbidity index; KPS, Karnofsky performance scale.

*Ten patients had a follow-up time of <2 years and were disease-free and alive at time of last follow-up, and hence were excluded from the long-term survivor and the short-term disease-free survivor groups.

6 months (range, 1-61) and a 4-year CIR of 28%. In the long-term survivor group, only 4 (3%) patients progressed. The median time to relapse in this group was 46 months (range, 36-61) and with a 4-year CIR of 2.9% (Figure 3). Among the patients who relapsed within 2 years of transplant, 73 patients died of their disease and 15 patients remain alive at their last follow-up. For the 4 patients who relapsed in the long-term survivor group, 2 patients died and 2 remain alive in remission at the date of last follow-up. None of the factors analyzed in Table 2 were found to predict relapse risk, likely due to the small number of events.

Relapse- and non-relapse mortality

One hundred and eighty-one (54%) patients died during the study period, of which 77 patients died of relapsed disease. The estimated 4-year NRM for all study patients was 30%, and the most frequent causes of NRM in all study patients were infections and GVHD. In the long-term survivor group, 13 (9%) patients died during the study period, of which only 2 (1%) died of relapsed disease. The estimated 4-year NRM in this group was 3.3% (Figure 3), and the most common cause of death was second primary malignancy (4 patients), all of which had non–small cell lung cancers (3 were heavy smokers). Other causes of death in the long-term survivor group included infection (n = 2) and 1 each from GVHD and sudden death. Table 3 summarizes causes of death for all patients and for the long-term survivors. None of the factors analyzed in Table 2 were found to predict NRM risk, likely due to the small number of events after 2 years.

GRFS

Table 1 summarizes the cumulative incidence rates of acute and chronic GVHD for all study patients and for those in the long-term survivor and short-term disease-free survivor groups. For all study patients, 10.75% developed severe acute grade 3-4 GVHD and 9.55% developed extensive chronic GVHD. Patients in the long-term survivor group had significantly lower rates of grade 3-4 acute GVHD compared with short-term survivors (4.22% vs 16.40%; $P = .004$), but the rates were not statistically significant for extensive chronic GVHD (12.68% vs 7.10% for long-term survivor vs short-term disease-free survivor groups; $P = .67$). Regarding GRFS, the 1-year and 2-year rates for all study patients were 45% and 39%, respectively (supplemental Figure 1A). For the long-term survivor group, the respective 1-year and 2-year

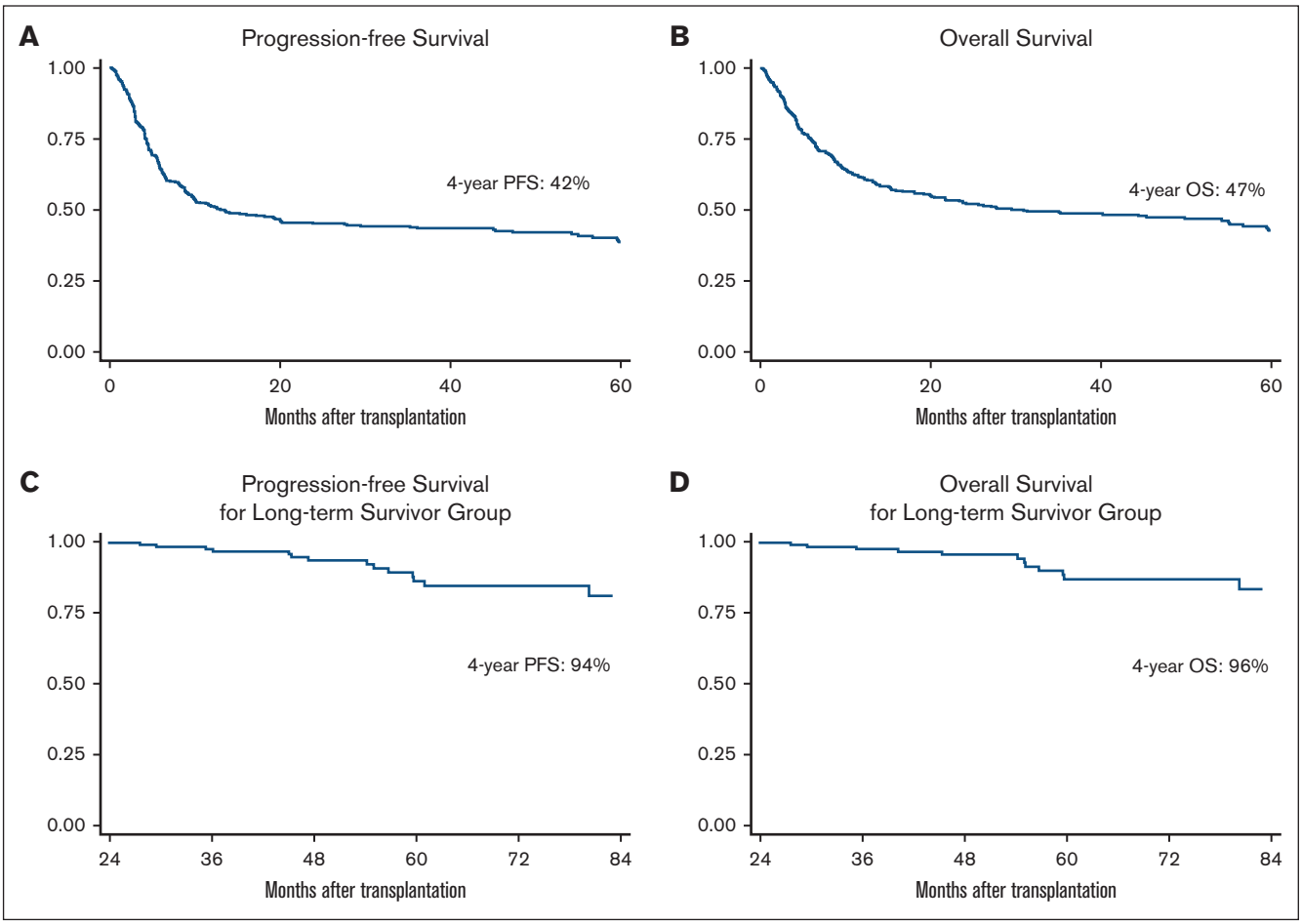

Figure 1. Progression-free survival and overall survival. PFS (A) and OS (B) for all study populations. PFS (C) and OS (D) for patients who are disease-free and alive at 2 years from transplant.

GRFS rates were 90% and 85%, compared with 29% and 8% in the short-term disease-free survivor group ($P < .0001$) (supplemental Figure 1B).

Discussion

Given the remarkable improvements in the outcomes of haplo-SCT over the past decade, haploidentical donors are increasingly being used as an alternative donor source in patients with high-risk hematologic neoplasms. To our knowledge, this is 1 of the largest single institutional studies to report on the long-term outcomes of patients who underwent unmanipulated haplo-SCT with PTCy–based GVHD prophylaxis. We report excellent long-term survival for patients who were alive and disease-free at 2 years after transplant, with 4-year PFS and OS rates of 94% and 96%, respectively. Furthermore, we noticed very low rates of relapse and relapse-related deaths in the long-term survivor group.

Several studies reported on long-term outcomes after allogeneic SCT, but majority focused on matched donors and only a few addressed conditional survival.[6-9] In 1 of the largest studies to report on conditional survival (87% of donors were matched related and the median follow-up was 80 months), the 5-year OS for patients who were alive and disease-free at 2 years was 89%.[6] A second large registry study, with a longer median follow-up of 9 years, showed a 10-year OS rate of 85%.[7] Both of these studies included predominantly matched related donors with a young patient population (median age <30 years). A more recent single institution study, included 389 patients, reported on conditional survival for patients who were alive and disease-free at 1 year. With a median follow-up of 48.2 months, the 5-year OS was 78%.[8] In this study, in contrast to the other aforementioned studies, patients were older (median age, 51 years) and donors were predominantly matched unrelated (39%), followed by matched related (37%), and haploidentical donors (24%). The findings from our report are very encouraging, showing an excellent long-term outcome for patients who underwent transplantation from alternative haploidentical donors. A more recent large registry study using the Center for International Blood and Marrow Transplant Research database compared the outcomes of SCTs for patients with acute leukemia and MDS who received haploidentical (n = 2036) vs matched unrelated donors (284); all patients received PTCy–based GVHD prophylaxis.[10] Interestingly, outcomes were favored in this study for matched unrelated SCT only in patients who received reduced intensity but not myeloablative conditioning. However, the median follow-up in this study was relatively short (1 year for matched

Table 2. Univariable analysis evaluating predictors of PFS, OS, NRM and relapse rate of the long-term survivor group

	N	PFS		OS		NRM		Relapse rate	
	144	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age									
<55 y	95	1		1		1		1	
≥55 y	47	3.409 (1.211-9.600)	.02	3.312 (1.078-10.180)	.037	2.475 (0.769-7.966)	.129	7.128 (0.693-73.312)	.099
Sex									
Male	82	1		1		1			
Female	60	0.416 (0.129-1.346)	.143	0.551 (0.168-1.812)	.327	0.679 (0.204-2.257)	.528	N/A	
Race									
White	63	1		1		1			
Asian	9	0.453 (0.049-4.172)	.489	0.707 (0.079-6.333)	.757	0.952 (0.073-12.353)	.970	N/A	
Black	35	0.536 (0.317-2.093)	.370	0.781 (0.194-3.152)	.729	1.130 (0.273-4.674)	.866	N/A	
Hispanic	32	0.607 (0.159-2.314)	.465	0.871 (0.217-3.488)	.845	1.277 (0.284-5.737)	.750	N/A	
Time from diagnosis to transplant									
<6 mo	38	1		1		1			
6-12 mo	37	0.922 (0.620-1.371)	.689	0.927 (0.615-1.396)	.927	1.457 (0.239-8.866)	.683	N/A	
>12 mo	67	0.964 (0.693-1.340)	.825	0.915 (0.650-1.290)	.915	1.439 (0.291-7.122)	.655	0.531 (0.079-3.555)	.514
Period of transplant									
Transplant 2009 to 2012	29	1		1		1		1	.329
Transplant 2013 to 2016	69	0.653 (0.215-1.982)	.452	0.713 (0.212-2.397)	.584	0.577 (1.79-1.860)	.357	1.001 (0.077-12.933)	
Transplant 2017 to 2019	44	0.587 (0.060-5.767)	.648	0.772 (0.073-8.210)	.830	N/A		5.163 (0.191-139.261)	
KPS									
90-100	92	1		1		1		1	
<90	39	1.749 (0.537-5.696)	.354	1.551 (0.409-5.885)	.519	1.048 (0.217-5.051)	.953	4.021 (0.563-28.718)	.165
DRI									
Low/intermediate	99	1		1		1		1	
High/very high	37	2.161 (0.748-6.242)	.155	2.097 (0.664-6.626)	.207	1.856 (0.547-6.230)	.321	2.752 (0.379-19.965)	.317
HCT-CI									
≤3	99	1		1		1		1	
>3	43	0.766 (0.240-2.447)	.654	1.013 (0.309-3.326)	.983	0.794 (0.227-2.780)	.718	0.719 (0.073-7.089)	.777
Patient-donor CMV									
Seropositive-seropositive	77	1		1		1		1	
Seropositive-seronegative	40	0.952 (0.290-3.128)	.936	0.920 (0.253-3.353)	.9	0.708 (0.195-2.568)	.6	0.914 (0.178-4.692)	.915
Donor Age									
<35 y	67	1		1		1		1	
≥35 y	75	0.795 (0.288-2.199)	.659	0.735 (0.246-2.188)	.580	0.759 (0.238-2.427)	.129	0.868 (0.124-6.065)	.887

HCT-CI, hematopoietic cell transplantation–specific comorbidity index; HR, hazard ratio; N/A, not applicable.

Table 2 (continued)

	N	PFS		OS		NRM		Relapse rate	
	144	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Donor/recipient gender									
Male/male	50	1		1		1		1	
Female/female	29	0.523 (0.106-2.607)	.431	0.863 (0.158-4.715)	.865	1.089 (0.180-6.567)	.926	N/A	N/A
Male/female	31	0.409 (0.079-2.108)	.286	0.682 (0.123-3.788)	.662	0.842 (0.159-4.450)	.840	N/A	N/A
Female/male	32	1.295 (0.392-4.282)	.671	2.077 (0.547-7.879)	.283	2.097 (0.452-9.723)	.344	0.495 (0.049-5.015)	.552
Donor/recipient relationship									
Parent/child	15	1		1		1		1	
Sibling/sibling	62	0.919 (0.101-8.294)	.940	0.640 (0.066-6.202)	.700	0.665 (0.71-6.228)	.721	N/A	N/A
Child/parent	65	2.635 (0.335-20.689)	.357	2.310 (0.291-18.351)	.428	1.745 (0.222-13.681)	.596	N/A	N/A
Anti HLA antibody									
No DSA	105	1		1		1			
Anti HLA class I Ab	16	1.119 (0.245-5.110)	.885	1.391 (0.298-6.484)	.674	1.744 (0.325-9.348)	0.516	N/A	N/A
Anti HLA class II Ab	9	0.900 (0.113-7.156)	.920	1.165 (0.145-9.373)	.886	1.431 (0.393-5.217)	0.587	N/A	N/A
Anti HLA class I and II Ab	12	0.598 (0.076-4.674)	.624	0.791 (0.100-6.280)	.824	0.995 (0.114-8.679)	0.996	N/A	N/A
Acute GVHD grades 2-4									
No	90	1		1		1		1	
Yes	52	1.031 (0.366-2.899)	.954	1.006 (0.328-3.080)	.992	0.889 (0.269-2.938)	.847	1.525 (0.231-10.047)	.661
Chronic GVHD at 2 years									
No	114	1		1		1		1	
Yes	28	1.642 (0.523-5.160)	.396	1.200 (0.328-4.392)	.782	1.646 (0.416-6.516)	.477	1.434 (0.148-13.922)	.756

HCT-CI, hematopoietic cell transplantation–specific comorbidity index; HR, hazard ratio; N/A, not applicable.

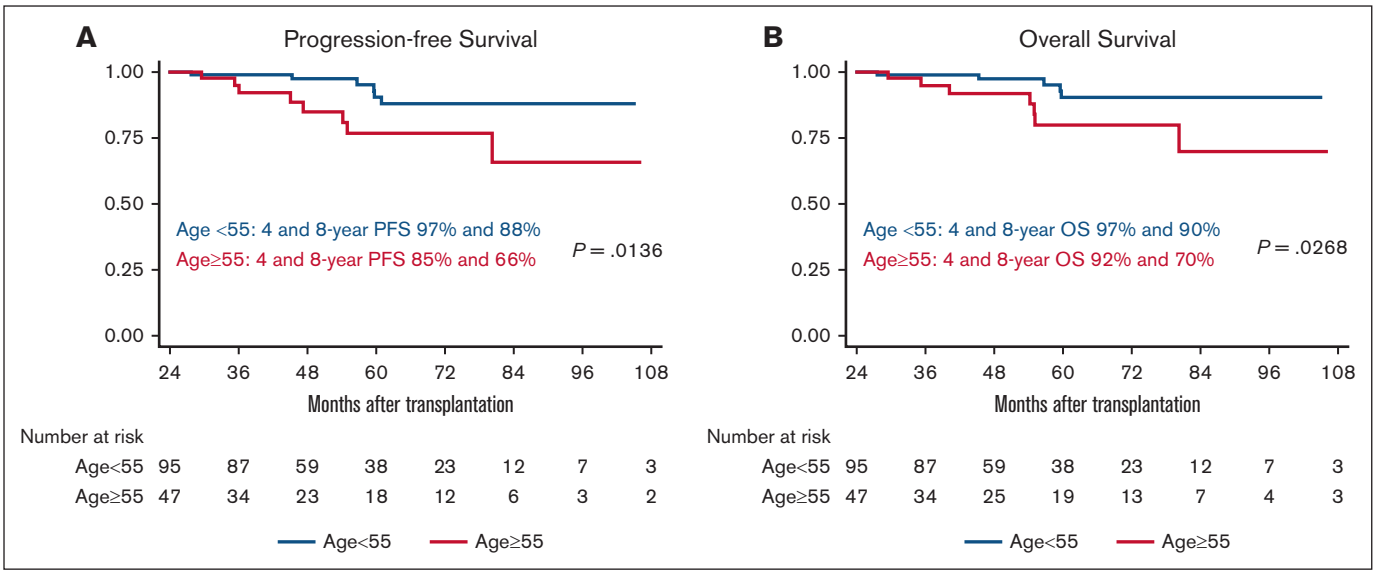

Figure 2. Progression-free survival and overall survival by age group. PFS (A) and OS (B) by age group for patients who are disease-free and alive at 2 years from transplant.

unrelated vs 2 years for haplo-SCT), and hence long-term outcomes could not be fully assessed.

Age is known to predict transplant outcomes, and until more recently, transplant was generally limited to younger fit patients. Most of published long-term data studies included younger patient populations.[6,7,9] In contrast, the median age in our study population was 48 years. In our multivariate analysis, age was the only predictive factor for both PFS and OS. For patients with age <55, the 4-year PFS and OS were 97% and 97%, respectively. Hematopoietic cell transplantation–specific comorbidity index and DRI were not predictive for long-term outcomes in our cohort, likely because most events (NRM and/or relapse) do occur in the first 2 years. Furthermore, GVHD was not predictive to long-term outcomes which can be related to low incidence of severe GVHD with PTCy–based GVHD prophylaxis and the improvements in GVHD treatments. However, longer follow-up might be needed to confirm the impact of cGVHD on long-term outcomes.

Relapse and NRM rates were low in our long-term survivor cohort. Only 3% relapsed after 2 years, and this is encouraging and somewhat favorable when compared with other studies that included predominantly matched donors.[6,7,9] Likewise, the 4-year NRM was low at 3.3%, however, longer follow-up is needed because several studies showed continued increased NRM over time with allogeneic SCT.[6,9,11] Similar to other studies, second primary malignancies and infections were among the most frequent causes of NRM. In contrast, we report lower rate of deaths related to GVHD which could be again attributed to the

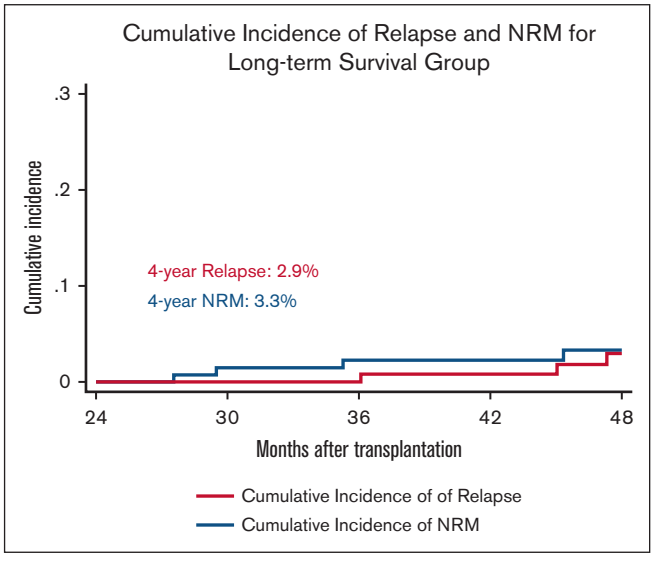

Figure 3. Cumulative incidence of NRM and relapse for patients who are disease-free and alive at 2 years from transplant.

Table 3. Causes of death

	All study patients	Disease-free and alive at 2 y
Cause of death		
Relapsed disease	77	2
Infections	27	2
GVHD	23	1
Organ failure	15	0
Pneumonia	12	0
Hemorrhage	6	0
Graft failure	5	0
Secondary malignancy	4	4
ARDS	4	0
Sudden death	1	1
Unknown	7	3
Total deaths	181	13

ARDS, acute respiratory distress syndrome.

use of PTCy, better GVHD treatments, and/or the need for longer follow-up. Likewise, we have not seen an increased risk of death from cardiovascular diseases, which might be related to the type of conditioning used (majority of patients in our cohort received reduced intensity conditioning) and improvements in management of cardiovascular diseases. Despite these encouraging outcomes, we acknowledge the need for longer follow-up and larger studies to better define the impact of using PTCy on the incidence of posttransplant second primary malignancies and cardiovascular diseases.

Our study is limited by its observational retrospective nature. Despite the relatively small sample size compared with registry cancer studies, to our knowledge, this is 1 of the largest single-center studies to report on long-term outcomes of unmanipulated haplo-SCT patients, all of which received PTCy–based GVHD prophylaxis. Given that the use of haplo-SCT with PTCy-based GVHD prophylaxis has only remarkably increased over the past decade, we have limited long-term follow-up beyond 10 years.

In summary, our findings suggest excellent long-term survival outcomes for patients who underwent haplo-SCT and were disease-free at 2 years after transplant. Late relapses were very low. Late NRM was mostly related to second primary malignancies and infections, and hence, the need for increased awareness and primary prevention strategies to further improve long-term outcomes.

Authorship

Contribution: S.A.S. devised the research and designed and performed the statistical analysis; S.S. contributed to statistical analysis and wrote the first draft of the manuscript; S.A.S. and S.S. contributed to data collection, analyzed and interpreted data, and wrote the manuscript; and S.A.S., S.C., U.P., J.R., Q.B., A.A., J.C., G.R., A.O., J.I., C.H., E.S., and R.C. contributed to the treatment of patients and critically reviewed and edited the manuscript.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

ORCID profiles: S.S., 0000-0002-4473-9216; S.C., 0000-0001-8597-3271; U.P., 0000-0002-7592-2224; Q.B., 0000-0002-4086-6453; A.O., 0000-0002-1669-0355; J.I., 0000-0002-5249-1177; R.C., 0000-0002-4314-5037.

Correspondence: Samer A. Srour, Department of Stem Cell Transplantation and Cellular Therapy, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd, Unit 423, Houston, TX 77030; email: ssrour@mdanderson.org.

References

1. Srour SA, Champlin RE, Ciurea SO. Alternative donor transplants: haploidentical hematopoietic stem cell transplantation. In: Kantarjian HM, Wolff RA, Rieber AG, eds. *The MD Anderson Manual of Medical Oncology, 4e*. McGraw Hill Education; 2022.
2. Martínez C, Gayoso J, Canals C, et al. Post-transplantation cyclophosphamide-based haploidentical transplantation as alternative to matched sibling or unrelated donor transplantation for Hodgkin lymphoma: a registry study of the Lymphoma Working Party of the European Society for Blood and Marrow Transplantation. *J Clin Oncol*. 2017;35(30):3425-3432.
3. Jones RJ. Is post-transplant cyclophosphamide a true game-changer in allogeneic transplantation: the struggle to unlearn. *Best Pract Res Clin Haematol*. 2019;32(4):101112.
4. Nunes NS, Kanakry CG. Mechanisms of graft-versus-host disease prevention by post-transplantation cyclophosphamide: an evolving understanding. *Front Immunol*. 2019;10:2668.
5. Arcuri LJ, Hamerschlak N, Rocha V, Bonfim C, Kerbauy MN. Outcomes after haploidentical hematopoietic cell transplantation with post-transplantation cyclophosphamide: a systematic review and meta-analysis comparing myeloablative with reduced-intensity conditioning regimens and bone marrow with peripheral blood stem cell grafts. *Transplant Cell Ther*. 2021;27(9):782.e1-782.e7.
6. Socié G, Stone JV, Wingard JR, et al. Long-term survival and late deaths after allogeneic bone marrow transplantation. late effects Working Committee of the International Bone Marrow Transplant Registry. *N Engl J Med*. 1999;341(1):14-21.
7. Wingard JR, Majhail NS, Brazauskas R, et al. Long-term survival and late deaths after allogeneic hematopoietic cell transplantation. *J Clin Oncol*. 2011;29(16):2230-2239.
8. Solh MM, Bashey A, Solomon SR, et al. Long term survival among patients who are disease free at 1-year post allogeneic hematopoietic cell transplantation: a single center analysis of 389 consecutive patients. *Bone Marrow Transplant*. 2018;53(5):576-583.
9. Martin PJ, Counts GW Jr, Appelbaum FR, et al. Life expectancy in patients surviving more than 5 years after hematopoietic cell transplantation. *J Clin Oncol*. 2010;28(6):1011-1016.
10. Gooptu M, Romee R, St Martin A, et al. HLA-haploidentical vs matched unrelated donor transplants with posttransplant cyclophosphamide-based prophylaxis. *Blood*. 2021;138(3):273-282.
11. Bhatia S, Dai C, Landier W, et al. Trends in late mortality and life expectancy after allogeneic blood or marrow transplantation over 4 decades: a blood or marrow transplant survivor study report. *JAMA Oncol*. 2021;7(11):1626-1634.