REGULAR ARTICLE

blood advances

Analysis of disparities in time to allogeneic transplantation in adults with acute myelogenous leukemia

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Key Points

- Time to transplant physician consult and allograft is delayed in non-European patients with AML.
- Cord blood facilitates rapid transplantation regardless of patient ancestry.

Although alternative donors extend transplant access, whether recipient ancestry affects the time to allogeneic transplant is not established. We analyzed the likelihood of clinically significant delays to allograft by patient ancestry in 313 adult patients with acute myelogenous leukemia (AML) who underwent transplantation. Non-European ancestry patients (n = 99) were more likely than Europeans (n = 214) to receive HLA-mismatched donor allografts (45% vs 24%). Overall, the median time from transplant indication to allograft was 127 days (range, 57-1683). In multivariable analysis, non-Europeans had an increased risk of prolonged indication to transplant time >180 days owing to significant delays in indication to consult >90 days and consult to transplant >120 days. Compared with recipients of HLA-matched unrelated donors (URDs), HLA-mismatched adult donor recipients were at an increased risk of delayed indication to transplant, whereas HLA-identical sibling and cord blood recipients were at a lower risk. Subanalysis showed more indication to transplant delays >180 days in non-European (44%) vs European (19%) 8/8 URD recipients. Finally, the pandemic further exacerbated delays for non-Europeans. In summary, although non-European patients with AML are less likely to receive 8/8 URDs as expected, if they do, their transplants are delayed. HLA-identical siblings and cord blood facilitate the fastest transplants regardless of patient ancestry, whereas other adult donor transplants are delayed. Strategies to mitigate referral barriers, hasten donor evaluation, and use all alternative donor sources are critical to ensure timely transplantation for patients with AML.

Introduction

Although allogeneic hematopoietic cell transplantation is curative for many patients with high-risk hematologic malignancies, racial/ethnic disparities can limit access to this specialized therapy. Most patients in need of allografts lack an HLA-identical sibling donor. Although 8/8 HLA-matched unrelated donors (URDs) are the preferred alternative donor source,[1] their availability is limited for

Submitted 15 July 2022; accepted 8 September 2022; prepublished online on *Blood Advances* First Edition 14 October 2022; final version published online 26 July 2023. https://doi.org/10.1182/bloodadvances.2022008572.

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Data are available on request from the corresponding author, Juliet N. Barker (barkerj@mskcc.org).

non-European–ancestry patients.[2] URD cord blood[3] (CB) and haploidentical[4] family donors both extend transplant access, and post-transplant cyclophosphamide-based mismatched URD (mmURD) transplantation has now emerged as an additional alternative.[5] However, disparities in access to each of these alternative graft sources persist.[6-8] For example, compared with European-ancestry patients, non-Europeans remain less likely to have an 8/8 HLA-matched URD[6] and have less access to CB units with higher $CD34^+$ content.[7] In addition, in a prospective clinical trial, our center demonstrated that African ancestry patients are less likely to secure a suitable haploidentical donor.[8] Recently, we analyzed 601 adult allograft recipients and found that although the use of all alternative donor sources (including CB, haploidentical, and mmURDs) is increasingly providing donors for all, significant disparities in access to "optimal" donors (ie, young adult donors and CB grafts of adequate dose and HLA match) persist for non-European ancestry patients.[9]

Although these data provide an insight into inequities in allograft provision, they do not account for disparities in the time to transplantation. Such an analysis is warranted given that delayed referral and/or donor provision can adversely affect transplant outcomes. Herein, we examined differences in the likelihood of clinically significant delays to transplant physician consultation and day of hematopoietic cell transplantation in a cohort of adult patients who were transplanted for acute myelogenous leukemia (AML), a uniform diagnosis that is a common allograft indication. We hypothesized that patients of non-European ancestry would be more likely to have delayed time from transplant indication to allograft resulting from the combined effects of delayed times from transplant indication to consult and consult to transplant.

Methods

Patient inclusion

This retrospective cohort analysis included all consecutive recent (1 January 2016 to 31 December 2021) first allograft recipients aged 19 to 70 years who were transplanted for AML in complete morphologic remission (n = 313). An analysis commencement date of January 2016 was chosen as this was when routine use of haploidentical related donors began in addition to HLA-identical sibling, 8/8 HLA allele-matched URD, and CB transplants at our center. The study was approved by the Institutional Review Board at Memorial Sloan Kettering Cancer Center and conducted according to the Declaration of Helsinki.

Transplant physician consultation and donor prioritization and identification

Patients were either referred for transplant physician consultation internally or by external providers. Ninety-seven patients in this analysis were enrolled on www.clinicaltrials.gov (#NCT02677064), a prospective observational study with the aim of facilitating consultation with a transplant physician during admission for AML induction (or reinduction) chemotherapy. During the study period, in the absence of an HLA-identical sibling donor, an 8/8 HLA allele-matched URD was prioritized, followed by either double-unit CB grafts or haploidentical grafts. CB grafts were generally preferred for patients <60 years of reasonable fitness with adequate renal function (to permit therapeutic cyclosporine levels early posttransplant), especially if the patient was at high risk of relapse. Mismatched (5/8 to 7/8) URDs have been added as an additional alternative more recently. All patients underwent an URD search (either preliminary or formalized) before being considered for an HLA-disparate graft.

Definitions

Ancestry was defined using published criteria, with non-European patients having full or part non-European origins based on a detailed kinship history of maternal and paternal ancestors by transplant staff.[10,11] Patients self-identified if they were Black and/or Hispanic. African patients included African Americans, Afro-Caribbeans, and African immigrants, whereas White Hispanic patients were those from Central and South America who self-reported themselves as both non-Black and Hispanic. The Hematopoietic Cell Transplant-Comorbidity Index (HCT-CI)[12] was used to classify comorbidities. Disease complete remission (CR) was defined morphologically as per 2017 European Leukemia Network (ELN) criteria,[13] with <5% blasts overall in the marrow closest to the transplant date. The prepandemic period was defined as the transplant indication date occurring before 15 December 2019 (3 months before the COVID-19 pandemic onset in New York), whereas the pandemic period was subsequently.

The transplant indication date was the date of morphologic diagnosis of acute leukemia if 2017 ELN criteria[13] intermediate or adverse-risk, and/or high-risk molecular mutations and/or secondary AML. Otherwise, it was the date of relapse if the patients were without these risk features initially. Transplant physician consultation date was defined as the date of the first visit with a transplant physician after the diagnosis of AML. Externally referred patients received their AML treatment outside Memorial Sloan Kettering Cancer Center.

We analyzed times from the date of diagnosis of the transplant indication to transplant physician consultation, consult to transplant, CR to transplant date, and overall indication to transplant date, by recipient demographics and donor type. Clinically significant delayed times were defined as time from transplant indication to transplant consultation >90 days, consult to transplant >120 days, CR to transplant >90 days (as per Frassoni et al),[14] and indication to transplant >180 days.

Statistical methods

Descriptive statistics were reported using median and range for continuous variables and frequency and percentages for categorical variables. Age and HCT-CI were stratified by the median. Differences in baseline characteristics by ancestry were assessed using Wilcoxon rank sum tests for continuous variables and Pearson χ^2 tests for categorical variables. Times from the date of transplant indication to consult, consult to transplant, CR to transplant, and indication to transplant were grouped as delayed or not. Logistic regression was used to perform univariable analyses to examine variables associated with delayed times to consult or allograft. Multivariable analyses used models including ancestry, donor type, and all variables significant in univariable analysis at $P \leq .1$. All analyses were performed in R version 4.0.5.

Results

Patient characteristics (all patients)

Patient characteristics are shown in Table 1. Of the 313 adult allograft recipients (median age, 56 years; range, 19-70), approximately two-thirds (68%) had European origins (67 northwestern, 59 eastern,

Table 1. Patient characteristics

Variable	Group	Overall, N = 313	European, N = 214	Non-European, N = 99	*P* value
Age, y	Median age (range)	56 (19-70)	60 (22-70)	49 (19-69)	<.001*
	≤56, n (%)	160 (51)	92 (43)	68 (69)	
	>56 y, n (%)	153 (49)	122 (57)	31 (31)	
Sex, n (%)	Male	163 (52)	118 (55)	45 (45)	.11
	Female	150 (48)	96 (45)	54 (55)	
2017 ELN criteria[13], n (%)	Favorable/intermediate	228 (73)	157 (73)	71 (72)	.76
	Adverse	85 (27)	57 (27)	28 (28)	
HCT-CI	Median score (range)	2 (0-11)	2 (0-8)	3 (0-11)	.028*
	0-2, n (%)	183 (58)	134 (63)	49 (49)	
	3+, n (%)	130 (42)	80 (37)	50 (51)	
AML induction regimen, n (%)	Cytarabine & anthracycline	243 (78)	161 (75)	82 (83)	.37
	Liposomal daunorubicin & cytarabine	24 (8)	17 (8)	7 (7)	
	Venetoclax & azacytidine	14 (4)	12 (6)	2 (2)	
	Other	32 (10)	24 (11)	8 (8)	
Referral type, n (%)	Internal	199 (64)	139 (65)	60 (61)	.5
	External	114 (36)	75 (35)	39 (39)	
Graft source†, n (%)	HLA-identical sibling	67 (21)	45 (21)	22 (22)	<.001*
	8/8 URD	149 (48)	117 (55)	32 (32)	
	CB	69 (22)	36 (17)	33 (33)	
	Haploidentical	17 (5)	8 (3.5)	9 (9)	
	mmURD	11 (4)	8 (3.5)	3 (3)	
Period, n (%)	Prepandemic	260 (83)	176 (82)	84 (85)	.6
	Pandemic	53 (17)	38 (18)	15 (15)	

**P* values denote significant differences.
†Twelve (43%) White Hispanic, 12 (51.5%) African, and 11 (40%) Asian-ancestry patients received HLA-disparate grafts.

26 southern, 52 mixed, and 10 European not otherwise specified) and one-third (32%) had non-European origins (28 White Hispanic, 23 African, 28 Asian, 3 Middle Eastern, and 17 mixed non-European).

Approximately one-quarter (n = 85, 27%) of patients had ELN 2017 adverse-risk disease. In nearly all patients (n = 292, 93%, with intermediate or adverse-risk AML, and/or high-risk mutations and/or secondary AML), the diagnosis was the transplant indication date. In 21 (7%) remaining patients, it was the date of relapse.

The median HCT-CI was 2 (range, 0-11). Induction was most commonly with cytarabine plus an anthracycline (n = 243, 78%). Just over one-third (n = 114, 36%) of patients were external referrals, and there was no difference in the proportion of non-European ancestry patients who were internal (60/199, 30%) vs external (39/114, 34%) referrals. Only 67 (21%) patients received HLA-identical sibling donors, nearly half (n = 149, 48%) received 8/8 URDs, and the remaining patients received CB (n = 69, 22%), haploidentical related donor (n = 17, 5%), or mmURD (n = 11, 4%) grafts. Of the haploidentical donors, most (14/17, 82%) were children of the recipients, with the remaining 3 being siblings.

Patient characteristics (subgroup analyses by recipient ancestry and donor type)

Characteristics of European and non-European ancestry patients, including distribution by donor type, are shown in Table 1 and Figure 1. Non-Europeans were younger than Europeans: median, 49 years (range, 19-69) vs 60 (range, 22-70); $P < .001$ (Figure 1A). Non-Europeans also had higher HCT-CI scores than Europeans: median, 3 (range, 0-11) vs 2 (range, 0-8); $P = .028$. Similar proportions of the 2 groups received HLA-identical sibling donor transplants. Over half of Europeans received an 8/8 URD transplant (117/214, 55%). By contrast, nearly half of non-Europeans (45/99, 45%) received HLA-disparate grafts compared with less than one-quarter (52/214, 24%) of Europeans, $P < .001$ (Table 1; Figure 1B-C). Other characteristics, including sex, disease risk, AML induction regimen, and referral type, were similar.

Comparing by donor type, CB recipients were younger than adult donor transplant recipients (median, 47 vs 60 years). Approximately half of CB (33/69, 48%) and haploidentical related donor (9/17, 53%) recipients had non-European ancestry compared with only 22 of 67 (33%) HLA-identical sibling and 32 of 149 (21%) 8/8 URD transplants (Figure 1B-C). Differences in the percentages of ELN 2017 adverse-risk disease were not significant: HLA-identical sibling, 19/67 (28%); 8/8 URD, 36/149 (24%); CB, 23/69 (33%); haploidentical, 5/17 (29%); and mmURD, 2/11 (18%). Other characteristics were similar.

Time to transplant: all patients

Median times to consultation and transplant and variables examined for an association with delay are shown in Tables 2 and 3,

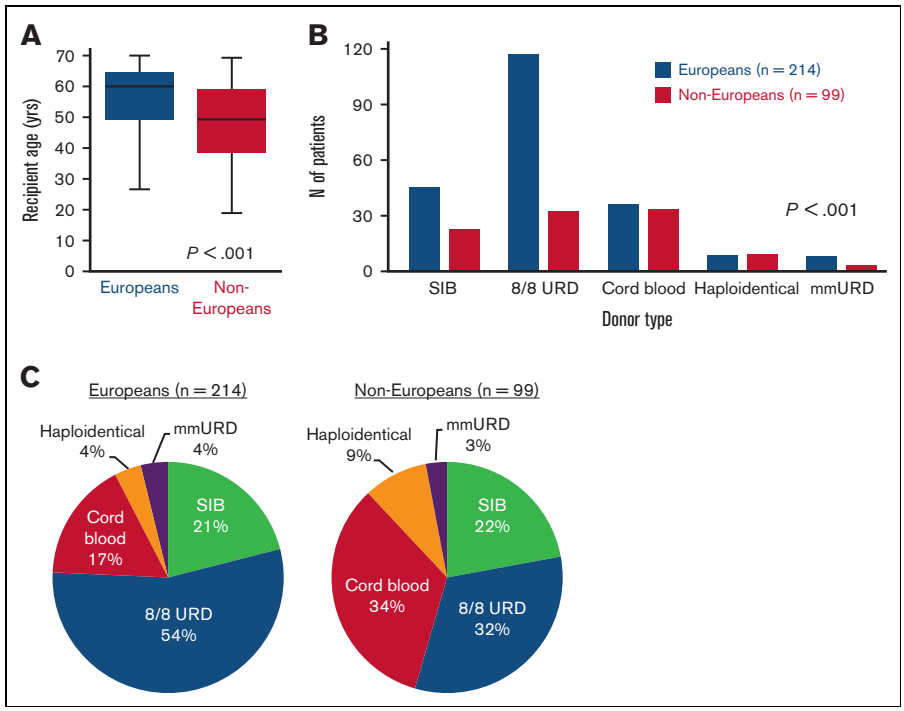


Figure 1. Distributions of the age and donor type of adult AML allograft recipients by ancestry (European vs non-European). Compared with Europeans (n = 214), non-European (n = 99) patients were younger (A) and more commonly received HLA-disparate grafts (B-C). Box plots in panel A present age medians (solid horizontal lines), interquartile range (IQR) (boxes), and range (bars). SIB, HLA-identical sibling.

respectively. Overall, the median times were: transplant indication to consult, 42 days (range, 1-1127); consult to transplant, 83 days (range, 13-1628); CR to transplant, 74 days (range, 9-1632); and indication to transplant, 127 days (range, 57-1683). Of the 313 patients, 17 (5%) (9 Europeans and 8 non-Europeans) had transplant indication to transplant time >450 days (range, 457-1683). Reasons included delayed referral (3/17), patient initially declining transplant (5/17), treatment complications (7/17), COVID-19–related (1/17), or another cause (1/17).

Overall, 43 of 313 (14%) patients had delayed transplant indication to consult, 71 of 313 (23%) had delayed consult to transplant, and 113 of 313 (36%) had delayed CR to transplant. This translated to approximately one-quarter of patients (75/313, 24%) having a clinically significant delayed indication to transplant of >180 days.

Time to transplant: associations with patient ancestry

As shown in Table 2 and Figure 2A, non-European ancestry patients had slower times from transplant indication to consult (48 vs 40 days), consult to transplant (87 vs 82 days), and CR to transplant (86 vs 70 days). This resulted in an indication to transplant of 145 days compared with 121 days in Europeans. Median speeds in White Hispanic (indication to consult, 52 days and indication to transplant, 160 days) and African (indication to consult, 56 days and indication to transplant, 150 days) ancestry patients were the slowest. Accordingly, as shown in Table 3, a significantly higher proportion of non-Europeans had delayed indication to consult, consult to transplant, and CR to transplant. Overall, one-third (33%) of non-Europeans had delayed transplant indication to transplant vs only 20% of Europeans, $P = .012$.

Time to transplant: associations with donor type

As expected, donor type was not associated with time to transplant consult but was significantly associated with subsequent and overall times to transplant (Tables 2 and 3). HLA-identical sibling and CB transplants had the fastest consult to transplant time (median, 77 and 73 days, respectively), compared with 86 days for 8/8 URD and >120 days for haploidentical and 5 to 7/8 URD transplants.

Overall, the median indication to transplant time was much shorter for HLA-identical sibling (119 days) and CB (121 days) transplants than for 8/8 URD (139 days), haploidentical (208 days), and 5/8 to 7/8 URD (154 days) transplants. Accordingly, HLA-identical sibling (12%) and CB (16%) transplants were the least likely to have delayed consult to transplant compared with 8/8 URD (24%), haploidentical (59%), and mmURD (55%); $P < .001$. A similar pattern was observed for transplant indication to transplant overall ($P = .004$).

When considering both ancestry and donor type (Figure 2B), among recipients of HLA-identical sibling donors, compared with Europeans, twice as many non-Europeans had delayed indication to transplant times, although this difference was not significant (median, 130 vs 111 days; delayed, 23% vs 11%; $P = .21$). Notably, however, non-European (vs European) 8/8 URD transplant recipients had markedly more delayed indication to transplant times (median, 168 vs 128 days; delayed, 44% vs 19%; $P = .004$). There was no difference in indication to transplant delays for non-Europeans vs Europeans when using CB grafts (median, 124 vs 112 days; delayed, 24% vs 19%; $P = .64$). Similar patterns were seen with consult to transplant delays: non-Europeans had over triple the proportion of delays among recipients of HLA-identical sibling donor transplants, although this difference was not

Table 2. Speed to transplant physician consult and transplant

Variable	Group	N	Median (IQR): indication to consult, d	Median (IQR): consult to transplant, d	Median (IQR): CR to transplant, d	Median (IQR): indication to transplant, d
Age, y	≤56	160	44 (20-65)	78 (62-106)	72 (36-100)	121 (99-162)
	>56	153	41 (18-67)	90 (66-122)	76 (37-112)	139 (108-189)
Sex	Male	163	42 (19-66)	83 (64-121)	76 (41-107)	127 (107-172)
	Female	150	45 (18-66)	84 (64-115)	70 (35-102)	126 (101-178)
Ancestry*	European	214	40 (17-65)	82 (63-105)	70 (36-96)	121 (104-159)
	Non-European	99	48 (27-82)	87 (69-130)	86 (38-140)	145 (114-214)
ELN 2017 risk[13]	Intermediate/ favorable	228	46 (20-74)	80 (63-115)	74 (36-112)	129 (103-168)
	Adverse	85	37 (17-55)	90 (71-115)	71 (40-99)	126 (106-182)
HCT-CI	0-2	183	45 (19-67)	82 (64-114)	71 (36-102)	124 (105-163)
	3+	130	39 (18-64)	87 (65-121)	78 (38-112)	130 (107-192)
Graft source	HLA-identical sibling	67	33 (18-65)	77 (64-107)	56 (35-89)	119 (101-145)
	8/8 URD	149	43 (19-63)	86 (69-119)	80 (41-114)	139 (107-177)
	CB	69	46 (29-67)	73 (57-93)	55 (31-92)	121 (93-155)
	Haploidentical	17	55 (19-71)	128 (76-212)	92 (66-165)	208 (120-271)
	mmURD	11	25 (15-102)	122 (80-147)	106 (72-154)	154 (123-202)
Referral type	Internal	199	32 (15-55)	90 (65-128)	64 (35-97)	124 (104-174)
	External	114	60 (37-89)	77 (58-94)	86 (52-130)	133 (108-178)
Period	Prepandemic	260	46 (20-66)	82 (63-115)	74 (37-104)	127 (105-177)
	Pandemic	53	32 (16-66)	86 (74-113)	72 (35-113)	131 (108-168)

*Median time (IQR) from transplant indication to transplant was 160 (123-241) days for White Hispanic, 150 (121-237) days for African, and 119 (98-168) days for Asian-ancestry patients.

Table 3. Variables associated with delayed times to transplant

Variable	Group	Indication to consult >90 d, N, %	*P* value	Consult to transplant >120 d, N, %	*P* value	CR to transplant >90 d, N, %	*P* value	Indication to transplant >180 d, N, %	*P* value
Age, y	≤56	21/160, 13	0.87	32/160, 20	0.3	55/160, 34	0.59	34/160,21	.3
	>56	22/153, 14		39/153, 25		58/153, 38		41/153,27	
Sex	Male	18/163, 11	0.2	42/163, 29	0.2	64/163, 39	0.27	37/163,23	.68
	Female	25/150, 17		29/150, 19		49/150, 33		38/150,25	
Ancestry†	European	21/214, 10	0.005*	40/214, 19	0.019*	66/214, 31	0.006*	42/214,20	.012*
	Non-European	22/99, 22		31/99, 31		47/99, 47		33/99, 33	
HCT-CI	0-2	22/183, 12	0.38	38/183, 21	0.41	63/183, 34	0.5	38/183, 21	.15
	3+	21/130, 16		33/130, 25		50/130, 38		37/130, 28	
Graft source	HLA-identical sibling	5/67, 7	0.11	8/67, 12	<0.001*	17/67, 25	0.024*	10/67, 15	.004*
	8/8 URD	20/149, 13		36/149, 24		62/149, 42		36/149, 24	
	CB	11/69, 16		11/69, 16		19/69, 28		15/69, 22	
	Haploidentical	3/17, 18		10/17, 59		9/17, 53		10/17, 59	
	mmURD	4/11, 36		6/11, 55		6/11, 55		4/11, 36	
Referral type	Internal	17/199, 9	<0.001*	56/199, 28	0.004*	59/199, 30	0.003*	47/199, 24	.9
	External	26/114, 23		15/114, 13		54/114, 47		28/114, 25	
Period	Prepandemic	32/260, 12	0.16	59/260, 19	>0.9	92/260, 35	0.7	63/260, 24	.9
	Pandemic	11/53, 21		12/53, 23		21/53, 40		12/53, 23	

**P* values denote significant differences.
†Time from transplant indication to transplant was >180 days in 10 of 28 (36%) White Hispanic, 9 of 23 (36%) African, and 5 of 28 (18%) Asian-ancestry patients.

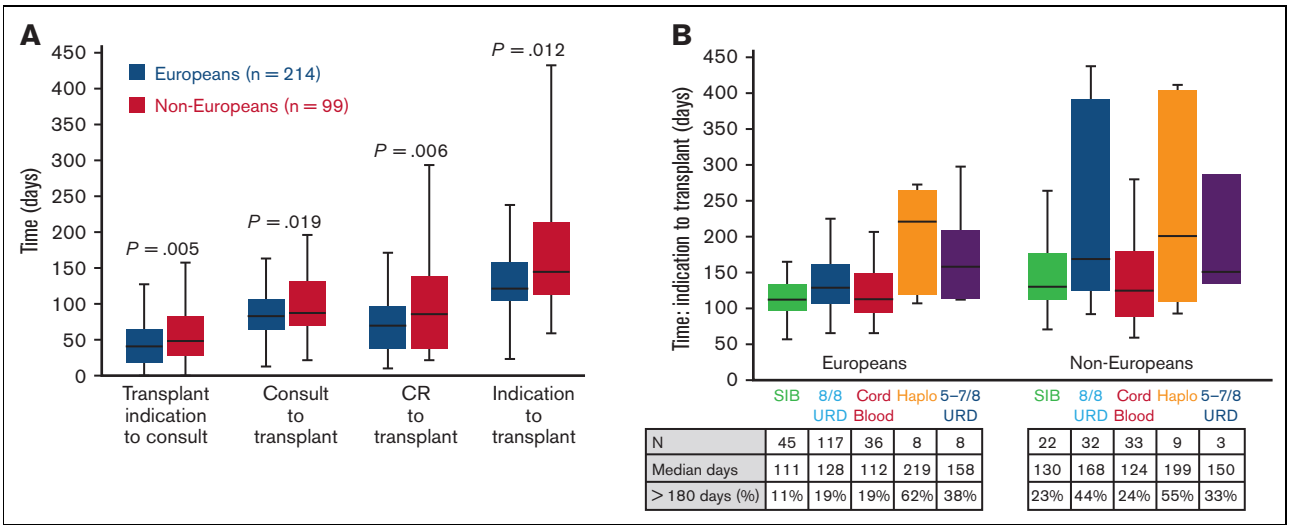


Figure 2. Time to transplant by patient ancestry and by donor type stratified by ancestry. (A) Compared with European ancestry patients, non-Europeans were more likely to have delayed times to transplant (ie, transplant indication to consult, consult to transplant, CR to transplant, and indication to transplant). (B) When analyzing time from transplant indication to allograft by donor type stratified by ancestry, HLA-identical sibling and CB transplants were the fastest regardless of ancestry, 8/8 URD transplants were markedly delayed in non-Europeans, and haploidentical and mmURD transplants were delayed in both groups. Box plots present time IQR (boxes), medians (solid horizontal lines), and range (bars). Maximum range outliers (17/313 patients) were excluded from this graphic. *P* values reflect differences in the likelihood of clinically significant delays to consult and transplant. Haplo, haploidentical.

significant (23% vs 7%, $P = .057$), and over double the proportion of delays among recipients of 8/8 URD transplants (44% vs 19%, $P = .003$), with no difference by ancestry among recipients of CB grafts (17% vs 15%, $P = .86$).

Time to transplant: associations with other factors

Compared with internal referrals, external referrals had slower times to consult (60 vs 32 days) with more delayed consults (23% vs 9%, $P < .001$) (Tables 2 and 3). However, external referrals had faster times from consult to transplant and a lower proportion of delays. Accordingly, time from indication to transplant (133 vs 124 days) overall and likelihood of delay (25% vs 24%, $P = .9$) were similar (Table 3). Finally, age, disease risk, and HCT-CI score were not associated with time to transplant.

Multivariable analyses of time to consult and transplant

Multivariable analysis is shown in Table 4. Non-Europeans had a greater likelihood of delayed times to consult, consult to transplant, and CR to transplant resulting in a greater likelihood of indication to transplant delay (odds ratio, 2.1; 95% confidence interval, 1.2-3.7; $P = .012$). Donor type had no association with time to consult but was significantly associated with the likelihood of delayed consult to transplant and overall indication to transplant. Compared with 8/8 URD recipients, likelihoods of delay were lower with HLA-identical sibling and CB transplants and higher with haploidentical and 5 to 7/8 URD transplants.

Impact of the pandemic on transplant speed by ancestry

When all patients were compared by prepandemic vs pandemic period, no delays to consult or transplant were detected (Table 3). However, when patients were split by their ancestry, the pandemic notably worsened delays for non-Europeans. Specifically, among the Europeans, the pandemic had no effect. By contrast, non-Europeans were delayed relative to the Europeans prepandemic, and this relative delay was even further exacerbated by the pandemic (Figure 3).

Discussion

Allograft literature is largely dedicated to analyzing transplant outcomes by diagnosis, conditioning/immunosuppressive regimen, or stem cell source. Although data have emerged demonstrating alternative donors extend transplant access, few studies have addressed disparities in time to referral and transplantation according to patient demographics and stem cell source. In this "real-world" analysis, we demonstrate multiple disparities from the standpoint of ancestry in the timely provision of allogeneic transplantation for patients with AML.

Firstly, we found relatively fewer older non-Europeans were transplanted, suggesting an intersectional disadvantage of older age for non-Europeans. Older age and non-White race have been linked to reduced allograft access[15] with 2 national cancer database analyses of younger[16] (18-60 years) and older[17] (61-75 years) patients with AML demonstrating similar findings. In addition, Dehn et al[18] reported that patients recorded as White were more likely to receive a transplant compared with those recorded as African American. Lack of referral is a likely contributor, with a survey of 113 US hematologists/oncologists identifying a greater likelihood of nonreferral in older and African American patients.[19]

Non-European (especially White Hispanic and African) ancestry patients were also more likely to suffer clinically significant delays to specialist consultation and allograft. In isolation or combination, these disparities are likely because of structural barriers delaying referrals,[19] socioeconomic barriers[20,21] especially for the Hispanic

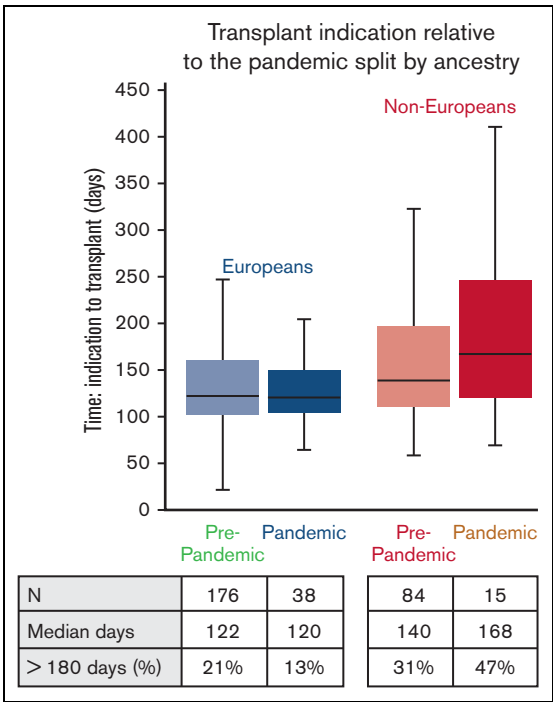
Table 4. Multivariable analysis of factors associated with delayed times to transplant

End point	Variable	Group	Odds ratio	95% confidence interval	*P* value
Transplant indication to consult >90 d	Ancestry	European	–	–	.005*
		Non-European	2.8	1.4-5.6	
	Donor type	8/8 URD	–	–	.11
		HLA-identical sibling	0.5	0.2-1.3	
		CB	0.8	0.4-2.0	
		Haploidentical	1.2	0.2-4.6	
		mmURD	4.6	1.1-17.9	
	Referral type	External	–	–	<.001*
		Internal	0.3	0.2-0.6	
Consult to transplant >120 d	Ancestry	European	–	–	.005*
		Non-European	2.4	1.3-4.5	
	Donor type	8/8 URD	–	–	<.001*
		HLA-identical sibling	0.3	0.1-0.8	
		CB	0.5	0.2-1.0	
		Haploidentical	3.3	1.1-10.2	
		mmURD	3.6	1.0-14.0	
	Referral type	External	–	–	.002*
		Internal	2.7	1.4-5.4	
CR to transplant >90 d	Ancestry	European	–	–	.001*
		Non-European	2.4	1.4-4.2	
	Donor type	8/8 URD	–	–	.002*
		HLA-identical sibling	0.4	0.2-0.8	
		CB	0.4	0.2-0.7	
		Haploidentical	1.4	0.5-4.0	
		mmURD	1.8	0.5-6.6	
	Referral type	External	–	–	<.001*
		Internal	0.4	0.3-0.7	
Indication to transplant >180 d	Ancestry	European	–	–	.012*
		Non-European	2.1	1.2-3.7	
	Donor type	8/8 URD	–	–	.010*
		HLA-identical sibling	0.5	0.2-1.0	
		CB	0.7	0.3-1.4	
		Haploidentical	3.7	1.3-11.0	
		mmURD	1.7	0.4-6.2	

**P* values denote significant differences.

and African ancestry groups,[22] and the pursuit of matched or mismatched adult donors that do not materialize because of donor attrition or ineligibility, and/or difficulties transporting grafts across international borders.[23] These findings are important as timely transplantation promotes posttransplant survival.[24] Moreover, optimizing prompt transplantation in older adults regardless of racial/ethnic origins is critical as treatment is expanded to this population.[25] Interestingly, transplants in non-Europeans were delayed even when using 8/8 HLA-matched URDs. This is explained by these patients having fewer HLA-matched donors with higher donor attrition[26,27] and reinforces the need to pursue many URDs simultaneously (even in the HLA-matched setting) as well as backup alternative donors, and to abandon unsuccessful URD searches early.

An additional challenge is that although HLA-mismatched adult donors extend transplant access to non-Europeans, the provision of these transplants is delayed. This compounds the disparity that we have recently reported that non-European patients without HLA-identical sibling donors received significantly older adult donors than their European counterparts, and their URDs were more mismatched.[9] Although this observation may not be surprising in recipients of mmURDs, we acknowledge that delays with haploidentical transplants in some patients were not expected. The reasons are likely multifactorial and could have been because of considering haploidentical donors after failed URD searches, these patients being older and more likely to have non-European ancestry, and greater difficulties in securing haploidentical donors for patients from racial /ethic minority groups (especially those of African



N	176	38	84	15
Median days	122	120	140	168
> 180 days (%)	21%	13%	31%	47%

Figure 3. Time from indication to transplant in European and non-European ancestry patients according to whether their transplant indication was in the prepandemic vs pandemic periods. Prepandemic was the transplant indication occurring before 15 December 2019 (3 months before the New York pandemic onset); the pandemic period was afterward. Relative to Europeans, non-European ancestry patients were delayed prepandemic. Delays were then further exacerbated by the pandemic, whereas no pandemic differences were observed in Europeans. Box plots present IQR (boxes), medians (solid horizontal lines), and range (bars). Maximum range outliers (17/313 patients) were excluded from this graphic.

ancestry).[8] Importantly, considering CB as a possible stem cell source did not delay haploidentical transplants as our center prioritizes unit quality and cell dose over HLA match in unit selection. Therefore, the adequacy of a CB graft can be immediately ascertained by review of the search and does not require unit confirmatory typing.

Importantly, in the absence of an HLA-identical sibling, our analysis revealed CB transplants were the fastest and, unlike 8/8 URDs, ancestry had no effect on time to transplant. CB grafts are known to be faster to procure than URD grafts,[18,28] and this remains true in the current era of "donors for all." In our analysis, CB transplant recipients were younger, and many preferentially received CB owing to high-risk disease. Although these recipient characteristics could contribute to a faster transplant, the rapid availability of a cryopreserved graft is a major advantage, especially for patients with late referral or minimal residual disease.[29,30] Despite this, CB grafts are underused,[31] which is troubling given the high disease-free survival in CB transplant recipients with acute leukemia reported in multiple series.[3,29,30,32]

Our data are even more relevant given the compromised adult donor supply chain triggered by the COVID-19 pandemic. As with the pandemic in general,[33,34] we observed non-European patients were disproportionately affected. These delays were likely multifactorial. Pandemic limitations in adult donor availability are because of adult donor infections, logistical challenges at collection sites and with transportation, and the necessity to cryopreserve adult donor products,[35] with additional barriers for non-European–ancestry donors.[36]

We acknowledge that patients who were not referred, or those who were referred but not transplanted (owing to aggressive disease, comorbidities, patient choice, or disease progression/complications that developed during the failed pursuit of adult donors) could not be accounted for. In addition, our analysis did not evaluate the relative contributions of delays from transplant indication to URD/CB search initiation or to adult donor identification; nor did it examine how many adult donors required evaluation/patient, or, for CB/haploidentical donor recipients, when the decision was made to abandon URD searches. In addition, our results could have been affected by patient preference, provider bias, or other differences in recipient demographics (including socioeconomic status, insurance, and/or distance from the center), and these are critical questions given that structural racism is a mediator of disparities in AML therapy.[37] Moreover, relatively small numbers of haploidentical and mmURD transplant recipients precluded subgroup analyses.

These limitations notwithstanding, our findings highlight the need for systematic efforts to maximize equitable provision of optimized allogeneic transplantation for non-European ancestry patients. Moreover, it should be recognized that the best stem cell source is the one with the best available graft characteristics, which facilitates transplant in the time required for optimal patient care. Strategies to mitigate referral barriers[38] (especially for older non-Europeans), including interventions to support patients with limited resources, poor insurance, low health literacy, and/or language or cultural barriers, improvement of operational efficiencies to ensure prompt patient/family member HLA typing and related donor evaluations, efficient URD searches (including evaluating URD search prognosis at search initiation and abandoning poor or futile searches),[39,40] and use of all alternative donors including CB are critical to ensure timely transplantation for all. Future detailed prospective multicenter studies[41] are warranted to investigate disparities in allograft provision and their clinical consequences in AML and other diseases by ancestry and donor type, including evaluation of the intersectional impact of race/ethnicity/ancestry and socioeconomic status and the impact of donor algorithms and search conduct, as well as to test interventions to address these challenges.

Acknowledgments

The authors thank the Memorial Sloan Kettering Cancer Center transplant coordinators for assisting in detailed patient ancestral evaluations and their diligent work in securing donors.

This work was supported in part by a grant from the National Cancer Institute, National Institutes of Health (grant P30 CA008748).

Authorship

Contribution: W.B.F. and J.N.B. designed the study, assembled and analyzed the data, and wrote the manuscript; J.F. and S.D. performed the statistical analysis; S.C., S.Q., and E.D. maintained the patient database and provided data; W.B.F., B.G., A.S., C.C.,

S.A.G., A.A.J., R.J.L., E.B.P., M.-A.P., D.P., B.C.S., R.T., J.W.Y., I.P., and J.N.B. provided patient care; and all authors interpreted the data, reviewed and edited the manuscript, and approved the submitted version of the manuscript.

Conflict-of-interest disclosure: B.G. has received research funding from Actinium Pharmaceuticals and serves on the data and safety and monitoring board for Synthetic Biologics, Inc. A.S. serves as a consultant at the Scientific Advisory Board of ExCellThera. S.A.G. has served as a consultant for Amgen, Actinium, Celgene, Johnson & Johnson, Jazz Pharmaceutical, Takeda, Novartis, Kite, and Spectrum Pharma and has received research funding from Amgen, Actinium, Celgene, Johnson & Johnson, Miltenyi, and Takeda. M.-A.P. has received honoraria from AbbVie, Bellicum, Bristol-Myers Squibb, Incyte, Kite (Gilead), Merck, Novartis, Nektar Therapeutics, and Takeda; serves on data and safety monitoring boards for Servier, Cidara Therapeutics and Medigene; serves on the scientific advisory boards of MolMed and NexImmune; and has received research support for clinical trials from Incyte, Kite (Gilead), and Miltenyi Biotec. C.S.S. has served as a paid consultant on advisory boards for Juno Therapeutics, Sanofi-Genzyme, Spectrum Pharmaceuticals, Novartis, Genmab, Precision Biosciences, Kite (Gilead), Celgene, Gamida Cell, and GlaxoSmithKline and has received research funds for clinical trials from Juno Therapeutics, Celgene, Precision Biosciences, and Sanofi-Genzyme. J.W.Y. owns equity in Merck, Pfizer, and Amgen. I.P. has received research funding from Merck and serves as a member on a Data and Safety Monitoring Board for ExCellThera. J.N.B. has received consultancy payments from Gamida Cell and the New York Blood Center and a research funding from Merck. The remaining authors declare no competing financial interests.

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