Utilization of allogeneic hematopoietic stem cell transplantation among patients with newly diagnosed acute myeloid leukemia in California: a population-based linked dataset study

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Received: April 26, 2024.
Accepted: August 19, 2024.
Early view: August 29, 2024.

https://doi.org/10.3324/haematol.2024.285648

Abstract

Acute myeloid leukemia (AML) often requires allogeneic hematopoietic cell transplantation (alloHCT) for cure, but historically alloHCT has been strikingly underutilized. Reasons for this remain uncertain at the population level. We examined alloHCT utilization over time and explored associations between demographic / healthcare factors and use of alloHCT by age group (adolescent / young adult [AYA] 15-39 years, adult 40-64 years, older adult 65-79 years) using a linked dataset merging the Center for Internatonal Blood and Marrow Transplant Research, the California Cancer Registry, and the California Patient Discharge Database. Eligibility included patients newly diagnosed with AML in California between 2001-2016 who received induction therapy and had no prior HCT. Multivariable Fine-Gray regression analyses were fitted separately across age groups. Among 7,925 patients with AML, alloHCT utilization increased over time across all age groups; however, in the most recent time period studied (2011-2016), utilization within two years of diagnosis remained lowest in older adults (13%) relative to adults (41%) and AYA (49%). Factors statistically significantly associated with lower alloHCT utilization were: 1) AYA: female sex, lower neighborhood socioeconomic status (nSES), uninsured or Indian Health Services (IHS) coverage; 2) adults: older age, male sex, non-Hispanic Black or Asian race and ethnicity, unmarried, lower nSES, uninsured or covered by Medicaid, Medicare, or IHS, higher comorbidity, and living 100+ miles from a transplant center; and 3) older adults: older age, Asian race, and unmarried. In conclusion, using a population-based linked dataset, we demonstrate that utilization of alloHCT among older patients newly diagnosed with AML remains low in California, and factors associated with utilization vary by age group.

Introduction

Approximately 20,000 people in the United States are diagnosed with acute myeloid leukemia (AML) each year, with fewer than 10% of new diagnoses occurring in children and adolescent / young adults (AYA), one-third in adults aged 40-64 years, and a majority occurring at those aged 65 years and older.[1,2] Therapeutic strategies for AML are guided by patient fitness and cytogenetic / molecular genetic risk stratification. Whereas induction / consolidation therapy alone may be sufficient for many patients with favorable-risk AML, patients with intermediate- and adverse-risk features commonly require allogeneic hematopoietic cell transplantation (alloHCT) to achieve leukemia cure.[3] Importantly, the proportion of patients with adverse-risk AML increases with age.[4]

Although AML represents the most common disease indication for alloHCT,[5] studies suggest that alloHCT is strikingly

under-utilized in AML, particularly among older adults.[6-9] Previous investigations defined factors associated with receipt of alloHCT, including age, race and ethnicity, and insurance type, but have been limited to cancer registry analyses that do not fully capture receipt of alloHCT or claims-based analyses of selected populations.[7,10,11] Other studies have used HCT registries to identify common variables within populations of transplanted patients, but lack the broader population of patients with transplant-eligible diagnoses who never undergo alloHCT.[12-15]

To address the limitations of each of these approaches, we used a novel linkage of population-based data from the California Cancer Registry (CCR), the California Patient Discharge Database (PDD), and the Center for International Blood and Marrow Transplant Research (CIBMTR)[16] to perform in depth analyses of alloHCT utilization among newly diagnosed patients with AML over time, with a secondary aim of identifying factors associated with receipt of alloHCT within 3 distinct age groups. We hypothesized that there would be variations in factors affecting utilization of alloHCT by age group; however, based on prior research, we expected that certain barriers such as race and ethnicity, insurance type, and socioeconomic status would be present across all age groups.

Methods

Data sources and study cohort

Details describing the CCR, PDD, CIBMTR, and linking methodology have been previously published.[16] Briefly, the CCR has served as California's population-based cancer surveillance system since 1988, collects cancer incidence on greater than 99% of new cancer cases, and harmonizes data from the regional cancer registries within the state.[17] The PDD includes diagnostic and procedure codes on all inpatient admissions from over 400 non-federal hospitals across the state of California, and has done so since 1991 when the California Department of Health Care Access and Information initially mandated such reporting.[18] The CIBMTR is a research collaboration between the NMDP and the Medical College of Wisconsin. It comprises a voluntary working group of approximately 420 centers worldwide contributing detailed data on allogeneic and autologous HCT, and cellular therapies.

The study population included all patients within the CCR who were diagnosed with an initial primary AML between 2001-2016 aged 15-79 years old and who had received AML induction therapy based on reported receipt of chemotherapy collected in the CCR. Patients 80 years and older or patients who were not reported to have received chemotherapy for AML were excluded, given that these patients rarely receive HCT and/or generally had a poor prognosis precluding HCT.[19] Patients who underwent autologous HCT for AML were excluded. Additional cohort selection criteria are described in *Online Supplementary Table S1*. This study was approved by the Institutional Review Boards of the University of California Davis Comprehensive Cancer Center, the California Committee for the Protection of Human Subjects, and the NMDP, and was determined to not be human subjects research by the National Cancer Institute.

Variables considered in multivariable analyses

Individual patients' characteristics were obtained from the CCR and included: age at diagnosis (by continuous measurement), sex, race and ethnicity, marital status, health insurance at diagnosis (categorized according to age group as defined below) and year of AML diagnosis. Elixhauser Comorbidity Index was calculated using admission data from the PDD.[20] A previously developed neighborhood socioeconomic status index (nSES) that incorporates information on education, poverty, employment, rental / housing information, and household income of the patient's census block group was used to determine nSES.[21] ArcGIS (v. 10.6, Redlands, CA, USA) was used to determine the distance in miles from the patient's residential ZIP code at diagnosis to the nearest transplant center. Rural and urban commuting area codes[22] were also included using the patient's ZIP code.

Statistical analysis

Descriptive characteristics and modeling were performed separately across three age groups: adolescents and young adults (AYA, age 15-39 years), adults (age 40-64 years), and older adults (age 65-79 years). A sensitivity analysis of alloHCT utilization using different age groups (15-59, 60-69 *vs.* ≥70 years) was also performed. Univariate and multivariable logistic regression analyses were conducted using Cox proportional hazards regression models, accounting for the competing risk of death using the methods of Fine and Gray.[23] Variables were tested for collinearity, and proportional hazard assumptions were evaluated for each model separately using the Schoenfeld Residuals Test.[24] Models were stratified on variables determined to be non-proportional. All variables described above were retained in the three models with the only difference being the categories used to analyze insurance coverage for older adults to account for the high percentage of Medicare coverage. $P<0.05$ was considered to be statistically significant.

Results

Baseline patients' characteristics

A total of 7,925 patients newly diagnosed with AML met inclusion criteria; 1,432 (18%), 3,678 (46%), and 2,815 (36%) were categorized as AYA, adults, and older adults, respectively (Table 1). Males outnumbered females in all age groups. The distribution by race and ethnicity differed across age groups with a greater proportion of Hispanic

(41%) than non-Hispanic White (37%) patients among the AYA, and the opposite pattern among older adults. Marital status also differed across age groups with 63% of AYA classified as unmarried compared with 35% of adults and older adults. More comorbidity (Elixhauser score ≥3) was seen in adults (30%) and older adults (37%) than AYA (18%).

Table 1. Baseline sociodemographic and treatment characteristics of newly diagnosed acute myeloid leukemia patients in California, stratified by age group at diagnosis, 2001-2016.

Characteristics	15-39 years Total=1,432 N (%)	40-64 years Total=3,678 N (%)	65-79 years Total=2,815 N (%)
Age in years, median	29	55	71
Sex			
Male	742 (51.8)	2,054 (55.8)	1,655 (58.8)
Female	690 (48.2)	1,624 (44.2)	1,160 (41.2)
Race and ethnicity			
Non-Hispanic White	535 (37.4)	2,024 (55)	1,874 (66.6)
Non-Hispanic Black	86 (6.0)	226 (6.1)	111 (3.9)
Hispanic	583 (40.7)	864 (23.5)	454 (16.1)
Asian	210 (14.7)	525 (14.3)	346 (12.3)
Other*	18 (1.3)	39 (1.1)	30 (1.1)
Marital status			
Married**	500 (34.9)	2,316 (63.0)	1,778 (63.2)
Unmarried	899 (62.8)	1,287 (35.0)	974 (34.6)
Unknown	33 (2.3)	75 (2.0)	63 (2.2)
Commuting area codes			
Rural	63 (4.4)	166 (4.5)	159 (5.6)
Urban	1,369 (95.6)	3,512 (95.5)	2,656 (94.4)
Neighborhood socioeconomic status			
Low	690 (48.2)	1,289 (35)	914 (32.5)
Medium	274 (19.1)	781 (21.2)	564 (20.0)
High	468 (32.7)	1,608 (43.7)	1,337 (47.5)
Insurance category			
Self-pay, not insured	41 (2.9)	94 (2.6)	24 (0.9)
Private	747 (52.2)	2,406 (65.4)	779 (27.7)
Medicaid	482 (33.7)	724 (19.7)	119 (4.2)
Medicare	34 (2.4)	257 (7.0)	1,804 (64.1)
With supplement	6	80	777
Without supplement	11	90	591
Medicare managed care	0	16	236
With Medicaid eligibility	17	71	200
Military	31 (2.2)	86 (2.3)	42 (1.5)
Indian/Public Health Services/County, NOS	57 (4.0)	33 (0.9)	11 (0.4)
Unknown	40 (2.8)	78 (2.1)	36 (1.3)
Elixhauser Comorbidity Index			
0	210 (14.7)	387 (10.5)	155 (5.5)
1-2	394 (27.5)	991 (26.9)	569 (20.2)
≥3	260 (18.2)	1,087 (29.6)	1,050 (37.3)
Unknown	568 (39.7)	1,213 (33.0)	1,041 (37.0)
Induction therapy			
Therapy NOS	36 (2.5)	147 (4.0)	189 (6.7)
Single-agent therapy	83 (5.8)	362 (9.8)	944 (33.5)
Multi-agent therapy	1,313 (91.7)	3,169 (86.2)	1,682 (59.8)
Year of diagnosis			
2001-2002	138 (9.6)	422 (11.5)	362 (12.9)
2003-2004	142 (9.9)	401 (10.9)	259 (9.2)
2005-2006	160 (11.2)	406 (11)	287 (10.2)
2007-2008	194 (13.5)	460 (12.5)	345 (12.3)
2009-2010	190 (13.3)	486 (13.2)	324 (11.5)
2011-2012	201 (14.0)	468 (12.7)	373 (13.3)
2013-2014	210 (14.7)	524 (14.2)	386 (13.7)
2015-2016	197 (13.8)	511 (13.9)	479 (17.0)

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Characteristics	15-39 years Total=1,432 N (%)	40-64 years Total=3,678 N (%)	65-79 years Total=2,815 N (%)
Distance to nearest transplant center in miles			
<50	1107 (77.3)	2,852 (77.5)	2,076 (73.7)
50-99	149 (10.4)	405 (11.0)	400 (14.2)
≥100	176 (12.3)	421 (11.4)	339 (12.0)
Median distance (SE); IQR	22.2 (1.3); 31.3	23.3 (0.8); 32.2	24.3 (1.0); 40
Receipt of allogeneic transplant			
No	764 (53.4)	2,396 (65.1)	2,594 (92.1)
Yes	668 (46.6)	1,282 (34.9)	221 (7.9)

SE: Standard Error; IQR: Interquartile Range; NOS: not otherwise specified. *Other includes Native Hawaiian Pacific Islander, American Indian and Alaskan Native, and Unknown race/ethnicity. **Includes common law / unmarried domestic partner.

Over 94% of patients across all age groups lived in urban areas. However, more AYA (48%) than adults (35%) or older adults (32%) lived in low SES neighborhoods. Insurance coverage was predominantly private (52%) or Medicaid (34%) in AYA, private (65%) or Medicaid (20%) in adults, and various forms of Medicare (64%) in older adults. Distance to nearest transplant center was similar across age groups with approximately 25% of patients living ≥50 miles from a transplant center.

Utilization of allogeneic hematopoietic cell transplantation over time

Over the time period studied, a total of 2,171 (27%) patients received an alloHCT: 668 (47%), 1,282 (35%), and 221 (8%) were AYA, adults, and older adults, respectively. The median time from AML diagnosis to alloHCT was six months, with 75% of alloHCT occurring within 11 months of diagnosis and 90% within 21 months. Utilization of alloHCT was identified from all three data sources (Figure 1): CIBMTR identified 85% of HCT; PDD identified an additional 13%; and the CCR identified an additional 2%. The cumulative incidence of alloHCT utilization increased across all age groups over time; however, the increase in incidence (measured at 2 years following diagnosis) from 2001-2005 to 2011-2016 was greatest among adults (24-41%) followed by AYA (37-49%), and least among older adults (2-13%) (Figure 2). The sensitivity analysis using different age group cut-offs revealed similar trends in alloHCT utilization over time (*Online Supplementary Figure S1*). However, this analysis revealed strikingly low utilization of alloHCT (5%) among patients aged 70-79 years even in the most recent time period studied.

Factors associated with receipt of allogeneic hematopoietic cell transplantation by age group

The results of each age-group multivariable analysis for alloHCT utilization are presented in Table 2. In the AYA population, low or middle nSES relative to high nSES, and lacking insurance or coverage by Indian Health Services (IHS) or county public healthcare relative to private insurance were associated with reduced rate of alloHCT utilization. In contrast, male sex and a more recent year of diagnosis were associated with increased rate of alloHCT utilization. Medicaid and Medicare health insurance violated proportional hazards assumptions and were included as stratification variables in the model.

In the adult population, older age, male sex, and unmarried status were associated with a lower rate of alloHCT utilization. AlloHCT was also lower among non-Hispanic, Black and Asian patients relative to White patients, those residing in low or middle nSES relative to high nSES, and those who were uninsured or covered by Medicaid, Medicare, or IHS relative to private insurance. Finally, the presence of comorbidities and living 100 miles or more from a transplant center were associated with a lower rate of alloHCT utilization.

In the older adult cohort, older age, unmarried status, and Asian race were associated with lower alloHCT utilization, while a more recent year of diagnosis was associated with a higher rate of utilization.

Discussion

Using a novel population-based linked database encompassing >99% of patients newly diagnosed with AML in California, we found that alloHCT utilization increased in all age groups over time. However, as recently as 2016, only 13% of older adults who received initial AML therapy ultimately underwent alloHCT within two years of diagnosis. This is substantially lower than in AYA or adults, where 53% and 44% of patients with AML underwent alloHCT, respectively. Despite numerous studies demonstrating that alloHCT is a viable curative option for older adults with AML,[8,25-27] these results suggest that transplantation remains markedly underutilized in this population. Unlike other studies investigating HCT utilization, our linkage of statewide cancer registry and hospitalization data with the CIBMTR provides what we believe to be the most complete capture of alloHCT in a large and diverse population-based cohort of US patients with AML.

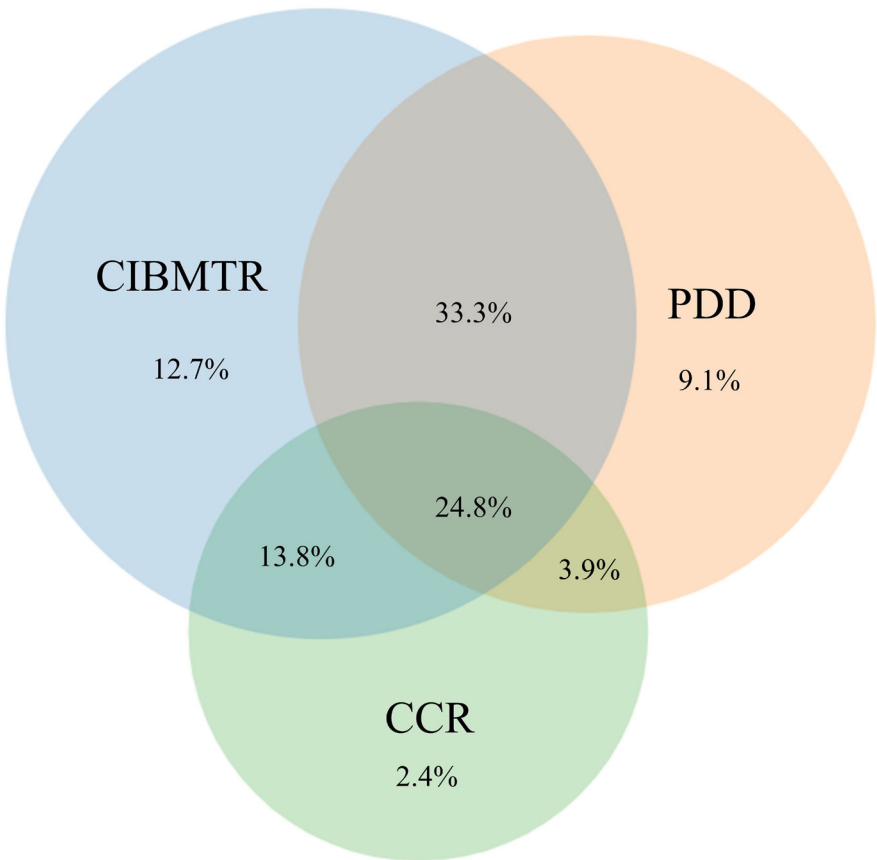

Figure 1. Registry source of allogeneic hematopoietic cell transplant data among newly diagnosed acute myeloid leukemia patients across California, 2001-2016. Three data sources, the California Cancer Registry (CCR), the Center for International Blood and Marrow Transplant Research (CIBMTR), and the California Patient Discharge Database (PDD), were used to identify the occurrence of allogeneic hematopoietic cell transplants for the entire cohort. The Venn diagram shows the percentage of transplants that are identified in each dataset and the overlap between the three datasets.

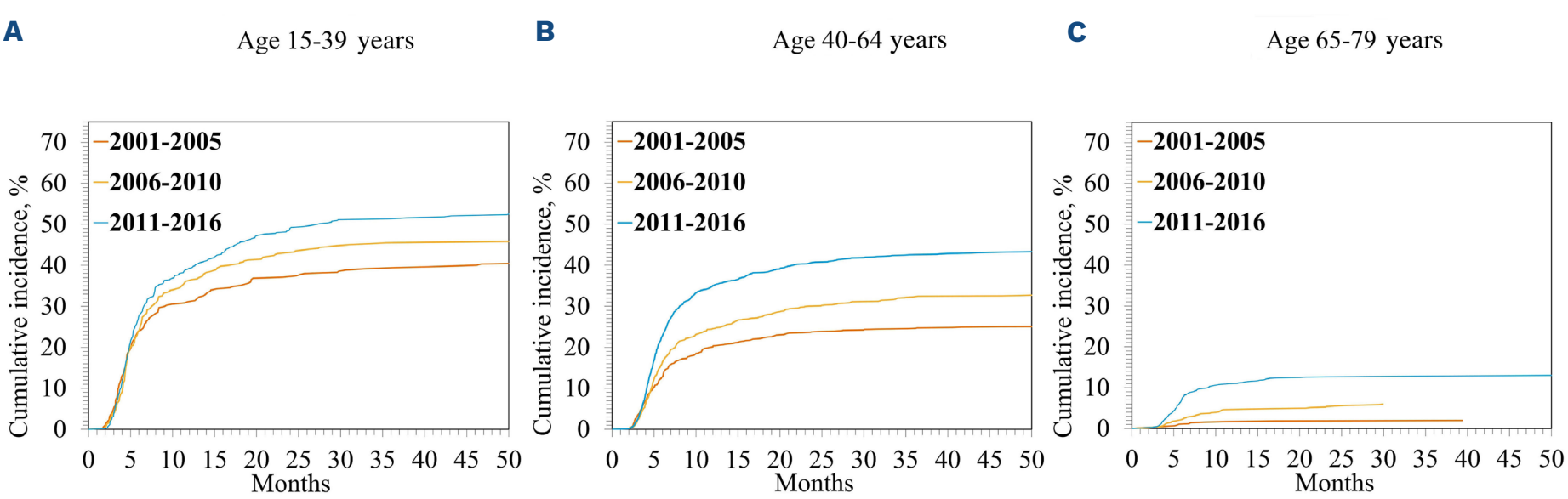

Figure 2. Cumulative incidence of allogeneic hematopoietic cell transplant utilization among newly diagnosed acute myeloid leukemia patients in California, by diagnosis era. The cumulative incidence of allogeneic hematopoietic stem cell transplant was calculated accounting for the competing risk of death for each age group: 15-39 years (A), 40-64 years (B), 65-79 years (C). The models were stratified by year of diagnosis grouped into three separate time periods: 2001-2005, 2006-2010, 2011-2016. Time was calculated from month of acute myeloid leukemia diagnosis.

The finding that alloHCT remains relatively rare among adults ≥65 years with AML is not new; yet it is concerning that in a population-based modern cohort such as ours, rates of alloHCT utilization in this age group remain far below expected. In this analysis, we limited the cohort to only patients with AML who received any type of induction therapy, thus reducing the potential of including older adults who received no treatment at all, which also remains an ongoing issue in AML.[19] Although we found that the use of alloHCT in this age group increased over time, more must be done to ensure that older adults are at least offered an opportunity to consider the risks and benefits of this therapy.

In our study, we were able to evaluate patient-related sociodemographic variables present in the cancer registry, which may influence whether a patient with AML receives an alloHCT. However, it is important to recognize that in the currently shifting landscape of AML therapy, a multitude of important variables that we were unable to examine, including response to therapy, induction tolerance, and immortal time bias, may factor into whether a patient with AML undergoes transplantation. Among the numerous

sociodemographic variables we were able to analyze, for older adults, we only found that being unmarried or Asian were associated with a lower rate of alloHCT. Previous studies have also suggested that older adults with strong

Table 2. Multivariable logistic regression analyses demonstrating characteristics associated with receipt of allogeneic-hematopoietic cell transplantation among newly diagnosed acute myeloid leukemia patients in California, stratified by age group.

Characteristics	15-39 years Total N=1,432		40-64 years Total N=3,678		65-79 years Total N=2,815	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Age at diagnosis (continuous)	1.00 (0.99-1.01)	0.854	0.97 (0.96-0.97)	<0.001	0.75 (0.71-0.80)	<0.001
Sex						
Female	Reference		Reference		Reference	
Male	1.17 (1.01-1.37)	0.041	0.81 (0.72-0.90)	<0.001	1.07 (0.68-1.69)	0.763
Race and ethnicity						
Non-Hispanic White	Reference		Reference		Reference	
Non-Hispanic Black	0.76 (0.51-1.11)	0.150	0.55 (0.40-0.75)	<0.001	0.79 (0.25-2.47)	0.684
Hispanic	0.98 (0.81-1.18)	0.813	0.92 (0.79-1.07)	0.262	0.59 (0.30-1.16)	0.123
Asian	1.18 (0.95-1.48)	0.141	0.83 (0.71-0.98)	0.025	0.47 (0.24-0.94)	0.033
Other/Unknown*	1.28 (0.68-2.41)	0.450	0.70 (0.36-1.36)	0.293	0.6 (0.07-5.26)	0.646
Marital status						
Married**	Reference		Reference		Reference	
Unmarried	0.92 (0.77-1.11)	0.395	0.82 (0.72-0.93)	0.002	0.55 (0.35-0.88)	0.013
Unknown	0.57 (0.33-0.98)	0.042	0.76 (0.50-1.17)	0.215	0.20 (0.02-1.71)	0.143
Commuting area codes						
Urban	Reference		Reference		Reference	
Rural	1.24 (0.81-1.9)	0.328	1.11 (0.80-1.53)	0.538	1.03 (0.36-2.95)	0.963
Neighborhood SES						
High	Reference		Reference		Reference	
Middle	0.74 (0.60-0.92)	0.006	0.76 (0.65-0.88)	<0.001	0.61 (0.35-1.08)	0.092
Low	0.70 (0.58-0.85)	<0.001	0.53 (0.46-0.62)	<0.001	0.67 (0.41-1.11)	0.118
Insurance coverage: AYA / adult						
Private/Military/Medicare with supplement	Reference		Reference		-	-
Self-pay, not insured	0.12 (0.04-0.39)	<0.001	0.43 (0.24-0.75)	0.003	-	-
Medicaid***	-	-	0.67 (0.57-0.79)	<0.001	-	-
Medicare****	-	-	0.73 (0.54-0.99)	0.040	-	-
Other public*****	0.59 (0.37-0.93)	0.024	0.33 (0.13-0.81)	0.016	-	-
Unknown	0.85 (0.52-1.39)	0.522	0.74 (0.49-1.13)	0.160	-	-
Insurance coverage: older adult						
Private	-	-	-	-	Reference	
Medicaid	-	-	-	-	0.45 (0.12-1.72)	0.243
Medicare without supplement	-	-	-	-	1.02 (0.54-1.93)	0.948
Medicare with supplement	-	-	-	-	1.44 (0.83-2.49)	0.196
Medicare managed care	-	-	-	-	0.79 (0.37-1.70)	0.549
Medicare Medicaid eligibility	-	-	-	-	1.22 (0.51-2.88)	0.658
Unknown/no insurance/self-pay	-	-	-	-	0.22 (0.02-2.71)	0.238
Elixhauser Comorbidity Index						
0	Reference		Reference		Reference	
1-2	1.01 (0.80-1.29)	0.908	0.79 (0.65-0.95)	0.014	0.86 (0.25-2.94)	0.809
≥3	0.76 (0.57-1.01)	0.054	0.59 (0.48-0.72)	<0.001	0.44 (0.13-1.51)	0.191
Unknown	0.87 (0.69-1.09)	0.227	0.8 (0.66-0.96)	0.018	0.74 (0.22-2.47)	0.629
Year of diagnosis (continuous)	1.03 (1.01-1.05)	0.001	1.08 (1.07-1.10)	<0.001	1.21 (1.15-1.28)	<0.001
Distance to nearest transplant center in miles						
<50	Reference	-	Reference	-	Reference	-
50-99	0.97 (0.75-1.26)	0.815	0.98 (0.81-1.19)	0.845	0.74 (0.38-1.43)	0.370
≥100	0.78 (0.59-1.02)	0.070	0.78 (0.64-0.95)	0.015	0.56 (0.27-1.14)	0.108

CI: Confidence Interval; HR: Hazard Ratio; N: number; nSES: neighborhood socioeconomic status; AYA: adolescents and young adults. Note: Multivariable Cox proportional hazard regression, accounting for the competing risk of death; treatment. *Other includes: American Indian / Alaskan Native and Pacific Islander. **Married including common law / unmarried domestic partner. ***Variable violated proportional hazard assumption and therefore stratified by Medicaid indicator. ****Medicare without supplement, administered through managed care, with Medicaid eligibility. Variable violated proportional hazard assumption and therefore stratified by Medicare indicator. *****Indian / Public Health Service, county-funded NOS.

social support are more likely to be offered alloHCT.[28-30] What our study was unable to uncover, which is important for understanding the reason for underutilization, is the proportion of older adults who were simply never referred or evaluated for alloHCT due to their age. We hypothesize that these are the major reasons for these patients not receiving potentially curative therapies. Specific nationwide interventions to educate and improve upon our findings may help in this regard. Further, with the recent shift towards more effective venetoclax-based induction regimens for older adults with newly diagnosed AML,[31-33] we hypothesize that the number of older patients who may benefit from consolidative alloHCT will continue to grow.

In addition to focusing on older adults, we identified sociodemographic characteristics associated with receipt of alloHCT by age group, demonstrating notable differences. For example, we found that both nSES and insurance coverage were particularly important in AYA and adult populations, but less so in older adults, where most patients with AML (>90%) were covered by either Medicare and/or private insurance. In California, very few patients with AML are listed as uninsured. However, one-third of AYA and 20% of adult patients in our cohort were covered by Medicaid, which was associated with lower rates of alloHCT utilization. Moreover, transplantation without insurance coverage at all is nearly impossible; thus, access to alloHCT may be more challenging in states that provide less expansive government-funded health insurance.[34] Poverty is a known barrier to cancer care;[35,36] the intersection of poverty and under-insurance is a critical barrier to alloHCT and is the focus of a variety of ongoing policy and research efforts.[37] Recent breakthroughs in the ability to safely transplant HLA mismatched donors led to a rise in haploidentical and HLA mismatched unrelated donor transplant.[38,39] This is particularly critical to ethnically diverse patients, where finding a suitable HLA-matched donor is substantially less common. Our study cohort reflected the racial and ethnic distribution of California residents, with 24%, 14%, and 5% of patients with AML identified through the registry as Hispanic, Asian, and Black, respectively. Our results demonstrate that Hispanic patients appear as likely as non-Hispanic White patients to receive alloHCT, which is reassuring, particularly given the large number of AYA described as Hispanic and the shifting demographics of California. However, our results also demonstrate that Asian and Black adults and Asian older adults were less likely to receive alloHCT than White patients. The causes of racial and ethnic disparities in accessing HCT are more complex than solely HLA disparities. Cultural background and influences have been previously reported to play a role in patients desire and ability to engage in shared decision-making as well as their opinions about transplant.[13,28,40-42] These differences can range from lowered health literacy and language barriers, personal belief systems and variation in values when it comes to treatment and outcomes, trust in the healthcare system and experiences with discrimination, and a patients desire to be involved in decision making.[42] In one study that looked at patients referred to HCT in the state of New York, European Americans were more likely to not receive HCT based on patient decision (20%) or stable disease (20%) compared to African Americans who were more likely to not receive an HCT due to physician decision or comorbidities (29%).[43] In the current era, where HLA is no longer a barrier to finding a suitable alloHCT donor, additional work is necessary to further understand patients' experiences with shared decision making, ensure patients are receiving information about treatment options that matches their language and health literacy needs, and educate physicians on best practices for providing culturally sensitive care to remove disparities in the uptake of alloHCT across different patient populations.

According to the Foundation for the Accreditation of Cellular Therapy (FACT), at least 16 centers perform alloHCT across the state of California.[44] Few studies have evaluated how distance to a transplant facility may impact access. We found that adult patients with AML living >100 miles from a transplant center were significantly less likely to receive alloHCT. While these patients were a relatively small proportion of our overall study cohort (12%), the inability to reach the transplant center, likely due to lack of referral or limited resources, are both important issues that extend beyond California to patients living in HCT "deserts" across the country. The American Society for Transplantation and Cellular Therapy and the NMDP have recently partnered to launch the ACCESS Initiative, which focuses on improving awareness, SES, and racial / ethnic inequities related to HCT and cellular therapies.[37] Our data suggest that patients living in HCT / cellular therapy facility "deserts" should be considered a vulnerable population who are significantly less likely to access HCT.

While our population-based linkage approach has several strengths, we recognize limitations associated with using cancer registry and hospitalization data to answer these questions. The CCR captures data on nearly all newly diagnosed AML patients in California, but the registry lacks consistent data on cytogenetic / molecular features and thus, we were unable to precisely characterize risk categories. However, data suggest that approximately 30% of patients with AML fall into European LeukemiaNet (ELN) "favorable" risk AML, with that proportion dropping in older adults to approximately 20%. Approximately 45% of patients have ELN "adverse" risk AML, rising to over 50% in older adults.[45] Given that alloHCT is indicated in first complete remission for adverse risk AML, for some patients with intermediate risk AML, and for previously un-transplanted patients in second complete remission regardless of risk category,[46] we would anticipate a large proportion of patients with AML across all of our studied age groups to have a disease indication for alloHCT. Similarly, we did not have detailed information from the CCR regarding AML induction

and response in our analysis, but we excluded patients who received no initial therapy for AML, as these patients would not typically be considered for alloHCT. Interestingly, we found no significant association between baseline comorbidity and receipt of alloHCT in older adults; this was counter to our hypothesis and may be explained by a host of factors including the comorbidity index in this analysis representing comorbidity at AML diagnosis, not following initial treatment, when HCT referral decisions often occur. Additionally, we recognize that many of our sociodemographic characteristics are proxies for more complex factors; for example, we used marital status as a proxy for social support, but certainly recognize that social support comes in many forms. Finally, this analysis focused on patients diagnosed with AML in California and may not be representative of other states.

In conclusion, despite observing an increase in alloHCT among patients with AML in California, transplant remains underutilized, particularly among older adults. As evidenced by the ACCESS Initiative and other endeavors, there is rising momentum to better understand, diminish, and ultimately eliminate barriers to accessing HCT and cellular therapies for patients with blood cancers and other diseases who may benefit from these therapies.[47] Systematically addressing these healthcare challenges across the transplant and cellular therapy ecosystem requires the concerted effort of key stakeholders.[48] Our data provide a benchmark of alloHCT utilization in the management of AML, and demonstrate the strength of linking datasets to uncover utilization rates of complex therapies.

Disclosures

JJA reports Advisory Boards for Ascella Health and Takeda. LM reports Advisory Boards / consulting for Kite, Autolus, Vor, Astellas, and Cargo.

Contributions

CLM primarily performed the analysis, conceptualized and designed the study, and drafted the manuscript. LM conceptualized and designed the study, and drafted the manuscript. THMK conceptualized and designed the study, provided valuable edits to the manuscript and approved the final version of the manuscript. AB, JJA, LMM, TW, SJS, BV, RA and RY provided valuable edits to the manuscript and approved the final version of the manuscript.

Funding

This work was supported in part by the Intramural Program of the National Cancer Institute (NCI) and by a contract from the National Cancer Institute (75N91019Q0116). TK is supported by the University of California Davis Comprehensive Cancer Center (P30CA093373) and by the National Center for Advancing Translational Science Grant UL1 0000860. The collection of cancer incidence data used in this study was supported by the California Department of Public Health pursuant to California Health and Safety Code Section 103885; the Centers for Disease Control and Prevention (CDC) National Program of Cancer Registries under cooperative agreement 5NU58DP006344; the NCI's Surveillance, Epidemiology and End Results Program under contract HHSN261201800032I awarded to the University of California, San Francisco, contract HHSN261201800015I awarded to the University of Southern California, and contract HHSN261201800009I awarded to the Public Health Institute. The ideas and opinions expressed herein are those of the authors and do not necessarily reflect the opinions of the California Department of Public Health, NCI, or CDC or their contractors and subcontractors. The CIBMTR is supported primarily by Public Health Service Grant U24CA076518 from the NCI, the National Heart, Lung and Blood Institute, and the National Institute of Allergy and Infectious Diseases; Grant HHSH250201700006C from the Health Resources and Services Administration; and Awards N00014-20-1-2832 and N00014-21-1-2954 from the Office of Naval Research. Support is also provided by NMDP Foundation, the Medical College of Wisconsin, the National Marrow Donor Program, and the following commercial entities: AbbVie, Actinium Pharmaceuticals, Adaptive Biotechnologies, ADC Therapeutics, Adienne SA, Allogene, AlloVir, Amgen, Anthem, Astellas Pharma US, AstraZeneca, Atara Biotherapeutics, BeiGene; bluebird bio, Bristol Myers Squibb, CareDx, CRISPR, CSL Behring, CytoSen Therapeutics, Eurofins Viracor dba Eurofins Transplant Diagnostics, Fate Therapeutics, Gamida-Cell, Gilead, GlaxoSmithKline, HistoGenetics, Incyte Corporation, Iovance, Janssen Research & Development, Janssen/Johnson & Johnson, Jasper Therapeutics, Jazz Pharmaceuticals, Kadmon, Karius, Kiadis Pharma, Kite Pharma, Kyowa Kirin, Legend Biotech, Magenta Therapeutics, Mallinckrodt Pharmaceuticals, Medac, Medexus Pharma, Merck & Co., Millennium Pharmaceuticals, Miltenyi Biotec, MorphoSys, Novartis Pharmaceuticals, Omeros, OptumHealth, Orca Biosystems, Ossium Health, Pfizer, Pharmacyclics, Priothera, Sanofi, Sanofi-Aventis US, Sobi, Stemcyte, Takeda Pharmaceuticals, Talaris Therapeutics, Terumo Blood and Cell Technologies, TG Therapeutics, Vertex Pharmaceuticals, and Xenikos BV.

Data-sharing statement

The data that support the findings of this study are available from the California Cancer Registry and the Center for International Blood and Marrow Transplant Research. Access to data is granted through an application process by the management or data custodians for each data resource.

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