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Quality of Care

Inferior Access to Allogeneic Transplant in Disadvantaged Populations: A Center for International Blood and Marrow Transplant Research Analysis



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Allogeneic hematopoietic cell transplantation (alloHCT) is offered in a limited number of medical centers and is associated with significant direct and indirect costs. The degree to which social and geographic barriers reduce access to alloHCT is unknown. Data from the Surveillance, Epidemiology and End Results Program (SEER) and the Center for International Blood and Marrow Transplant Research (CIBMTR) were integrated to determine the rate of unrelated donor (URD) alloHCT for acute myelogenous leukemia (AML), acute lymphoblastic leukemia (ALL), and myelodysplastic syndrome (MDS) performed between 2000 and 2010 in the 612 counties covered by SEER. The total incidence of AML, ALL, and MDS was determined using SEER, and the number of alloHCTs performed in the same time period and geographic area were determined using the CIBMTR database. We then determined which sociodemographic attributes influenced the rate of alloHCT (rural/urban status, median family size, percentage of residents below the poverty line, and percentage of minority race). In the entire cohort, higher levels of poverty were associated with lower rates of alloHCT (estimated rate ratio [ERR], .86 for a 10% increase in the percentage of the population below the poverty line; $P < .01$), whereas rural location was not (ERR, .87; $P = .11$). Thus, patients from areas with higher poverty rates diagnosed with ALL, AML, and MDS are less likely patients from wealthier counties to undergo URD alloHCT. There is need to better understand the reasons for this disparity and to encourage policy and advocacy efforts to improve access to medical care for all.

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INTRODUCTION

For many patients with hematologic malignancies or non-malignant diseases, allogeneic hematopoietic cell transplantation (alloHCT) is the preferred treatment option. Numerous

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factors influence whether a patient eligible for transplantation actually go on to undergo transplantation. Patients need to have a disease status that renders them eligible for alloHCT, have suitable performance status and organ function, and have an available donor. In addition, various sociodemographic variables, such as insurance coverage, might impair access to alloHCT [1]. A literature review conducted by Majhail et al [2] in 2000 summarized the factors that might influence access to alloHCT and broadly categorized them into 5 groups: donor availability, social, economic, provider, and health care system. The degree to which these factors, particularly socioeconomic factors, might influence the access to alloHCT is unknown.

One small study examining access to stem cell transplantation in Canada found rural patients were somewhat less likely to receive an autologous HCT compared with urban patients, although this difference was not statistically significant, possibly due to small numbers [3]. A recent study found that the majority of Americans are located within reasonable driving distance of a stem cell transplantation center (78.6% within a 90-minute drive, 94.7% within a 180-minute drive) [4]. Although that study might suggest that physical geography is not a significant barrier to transplantation, it did not attempt to compare transplantation rates between rural and urban Americans, or to examine how transplantation rates vary by other sociodemographic variables. An abstract presented at the most recent transplantation and cellular therapy meeting found that residents of Virginia diagnosed with AML were less likely to undergo transplantation if they were from a region with a higher proportion of African Americans [5]. In solid organ transplantation, multiple studies have shown inferior access to transplantation in patients living in rural areas and patients of disadvantaged sociodemographic status [6–8]. This research has not been replicated in alloHCT.

Multiple studies have shown that patients from disadvantaged areas might have inferior outcomes after alloHCT. Loberiza et al [9] compared outcomes of patients in the CIBMTR database by different sociodemographic attributes (income, rural/urban status) and found no difference in overall survival. In contrast, Khera et al [10] found that patients residing further away from a transplantation center who underwent nonmyeloablative transplantation might have inferior outcomes. However, neither of those studies attempted to compare access to transplantation of different sociodemographic groups.

In the present study, we sought to understand how the rate of alloHCT varied by rural/urban status, socioeconomic status, and racial composition of the county of residence at the time of diagnosis. Because data on the location of primary residence were lacking for patients undergoing related donor alloHCT, we focused on unrelated donor (URD) alloHCT as a potential surrogate for access to transplantation overall.

METHODS

This study integrated data from the Center for International Blood and Marrow Transplant Research (CIBMTR) and the Surveillance Epidemiology and End Results (SEER) program maintained by the National Cancer Institute (NCI) [11,12]. The CIBMTR is a research affiliation between the National Marrow Donor Program (NMDP)/Be The Match and the Medical College of Wisconsin comprising a voluntary working group of more than 450 transplantation centers worldwide that contribute detailed data on consecutive alloHCT and autologous HCT to a Statistical Center at the Medical College of Wisconsin in Milwaukee and the NMDP Coordinating Center in Minneapolis. Participating centers are required to report all transplantations consecutively. Mandatory reporting of data on all transplantation recipients to the CIBMTR results in universal capture of transplantation activity in the United States [12]. The SEER program maintains a population-based database of cancer incidence and survival covering 612 counties in 15 states, representing approximately 28% of the US population. In the SEER coverage area, all new diagnoses of malignancy are required to be reported, resulting in a

comprehensive, population-based database of cancer incidence. The 3 most common malignant indications for alloHCT are acute myelogenous leukemia (AML), acute lymphoblastic leukemia (ALL), and myelodysplastic syndrome (MDS) [11]. Data on the incidence of AML, ALL, and MDS were abstracted from SEER, and data on transplantation activity were abstracted from the CIBMTR.

All patients with a diagnosis of ALL, AML, or MDS recorded between January 1, 2000, and December 31, 2009 were included in this study. Date of diagnosis, rather than date of transplantation, was used to determine eligibility for inclusion in the cohort, because date of transplantation was not available in the SEER dataset, whereas the date of diagnosis was included in both databases. Because alloHCT was uncommon among patients age >65 during the study period, the analysis was restricted to patients age <65 [9].

The primary variable through which the patient residence is captured in the CIBMTR database is the ZIP code. Although ZIP code was captured for a majority of patients undergoing URD alloHCT, ZIP code data were incomplete for patients undergoing related donor alloHCT; therefore, this analysis was restricted to recipients of URD alloHCT. The indications for related donor and URD transplantation are similar, and we hoped to use access to URD alloHCT as a surrogate for access to all alloHCT in general. Potential causes for differential access to related donor or URD transplantation are family size and race/ethnicity. To account for this, the average family size of each county was captured and incorporated in the analysis. A sensitivity analysis restricted to white patients was completed to ensure that any difference in access reflects barriers to alloHCT other than differences in donor availability among minority populations.

For each of the 612 counties reporting data to SEER, the number of new incident cases of AML, ALL, and MDS between January 1, 2000, and December 31, 2009, was retrieved from SEER. From the CIBMTR, the number of URD alloHCTs performed in patients with ALL, AML, and MDS with a date of diagnosis over the same time period and geographic area was obtained. The date of diagnosis, not the date of transplantation, served as the inclusion criteria in both cohorts, to ensure that the transplantation activity corresponded with the SEER data. Thus, for each of the 612 counties covered, a transplantation rate was calculated as the number of transplantations performed divided by the number of new diagnoses. Next, a number of descriptive attributes were chosen to describe the sociodemographic makeup of that county. First, we determined the percentage of the county's population with a median income below the poverty line in 2000, from the US Census conducted in 2000 [13]. Race was included by examining the percentage of the county population in the year 2000 belonging to racial groups other than white alone (including black, American Indian/Alaska Native, Asian/Pacific Islander, and Hispanic). The Rural-Urban Continuum Code (RUCC) was used to categorize counties into 9 groups based on population size and proximity to a major urban center [14]. These 9 groups were then collapsed into 3 groups: metropolitan, >50,000 residents; micropolitan, 20,000–50,000 residents; and rural, <20,000 residents.

The rate of alloHCT in the 612 counties covered by SEER was compared using univariate and multivariate analysis. The ERR was calculated for all county attributes, comparing the transplantation rate for each attribute against that of a baseline group. Poisson regression was used to compare the rates of transplantation in rural and urban counties after adjusting for other possibly significant covariates. Racial/ethnic composition of the county, poverty rate, and average family size were examined in the model. A backward elimination model selection procedure was used to identify statistically significant covariates to be added into the model. A generalized linear mixed model framework allowed us to treat county as a random effect with specific correlation structure in which correlation between 2 observations depends on the distance between them. The Euclidean distance between counties is computed based on the coordinates (latitude and longitude) of the center of each county.

The primary analysis cohort consisted of all patients with ALL, AML, and MDS. In addition, there were three preplanned sensitivity analyses. First, as mentioned earlier, an analysis restricting both the number of diagnoses and the number of transplantations to white patients was done, to eliminate any bias introduced by differential availability of unrelated donors among different racial groups. Next, an analysis was done restricting the study population to only AML, to provide for a more homogenous study population. Finally, an analysis was done restricting the population to only pediatric patients (age <18 years at time of diagnosis) with ALL, to examine any differences in access among pediatric patients.

A statistical significance (α) level of .05 was used throughout. All statistical analyses were performed using SAS statistical software (SAS Institute, Cary, NC).

RESULTS

There were 30,468 new incident diagnoses of ALL, AML, and MDS in the SEER database. A total of 3147 patients in the

CIBMTR dataset met our inclusion criteria (Tables 1 and 2). The estimated ZIP code completeness was 75%. The overall rate of URD alloHCT was 10.3% in patients age <65 diagnosed with ALL, AML, or MDS.

In univariate analysis, the only significant predictor of transplantation rate was the percentage of residents below the poverty line (ERR, .84 for each 10% increase; $P = .0007$) (Table 3). There was no significant difference in transplantation rate among rural, micropolitan, and metropolitan counties ($P = .07$). Similarly, there was no difference in transplantation rate with variation in the percentage of minority residents (ERR, .98 for each 1-point increase in percentage of minority residents; $P = .09$). Finally, the median family size of the county was also not associated with a difference in transplantation rate (ERR, .77 for each person increase; $P = .10$).

Our final multivariable model included the percentage of the county population with an income below the poverty level because it was significant in the univariate analysis. Rural/urban status was forced into the model, because it was one of the factors of primary interest. A higher percentage of individuals below the poverty line remained significantly associated with a lower transplantation rate (ERR, .86 for each 10% increase; $P = .003$), whereas location of residence was not ($P = .24$) (Table 4).

Results of the sensitivity analysis restricted to patients with AML were similar to those for the entire cohort (Table 5). In multivariate analysis, the most important predictors of low transplantation rate was the percentage of county residents below the poverty line and the geographic location of the

Table 2
Descriptive Statistics for Continuous Variables

Category	Median (Range)
Poverty rate, % residents below the poverty line	17.5 (3.2–40.3)
Percent minority, % minority residents	15.3 (1.1–84.9)
Median family size, n	3.03 (2.49–3.88)

country (rural versus urban). These results were replicated in the analysis restricted to white Americans, among which we found that rural location and high levels of poverty were associated with lower transplantation rates. Results were different in the pediatric ALL cohort, with neither rural/urban location nor poverty rate associated with transplantation rate. In all multivariable models in the sensitivity cohorts, minority status and family size were not significant.

Finally, to ensure that URD alloHCT was a reasonable surrogate for alloHCT in general, we compared recipients of related donor and URD alloHCT in the CIBMTR dataset. We found no significant differences in characteristics reviewed (ie, disease, disease status at time of transplantation, year of transplantation, disease risk status, and patient age).

DISCUSSION

Several previous studies have attempted to compare outcomes following alloHCT based on sociodemographic factors, but to our knowledge, this is the first study aiming to explore sociodemographic factors influencing access to URD alloHCT. Given the important role of alloHCT in the treatment of hematologic malignancies (particularly AML and MDS), it is essential that all eligible patients have access to alloHCT, regardless of location of primary residence, income, or racial group. Studies examining outcomes following alloHCT are restricted to patients with sufficient resources to proceed to transplantation and might not be representative. Thus, although research studying outcomes following alloHCT in disadvantaged groups is important, it is equally important to ensure that patients in these groups actually have access to transplantation.

In this study, we found that patients diagnosed with AML, ALL, and MDS were significantly less likely to undergo URD alloHCT as a part of their treatment if they lived in areas with higher poverty rates. The lower rates of transplantation among patients residing in counties with higher poverty rates were seen in the main cohort and in all sensitivity cohorts except pediatric ALL. The impacts of other sociodemographic variables were less consistent. Although rural location was associated with lower rates of transplantation in some cohorts (AML diagnoses), it was not significant in any multivariable model.

Table 1
Transplantation Rate by County Attributes

Category	URD Allo-HCT Rate, %
Rural/urban	
Metropolitan (>50,000 residents)	8.77
Micropolitan (20,000–50,000 residents)	8.93
Rural (<20,000 residents)	7.54
Poverty rate	
Highest quartile (most poverty) (22.5%–40.3% residents below the poverty line)	7.44
50%–75% quartile (17.5%–22.5% residents below the poverty line)	7.39
25%–50% quartile (12.7%–17.5% residents below the poverty line)	10.16
Lowest quartile (least poverty) (3.2%–12.7% residents below the poverty line)	11.73
Minority rate	
Highest quartile (most minorities) (34.3%–84.9% minority residents)	7.17
50%–75% quartile (15.3%–34.3% minority residents)	8.33
25%–50% quartile (5.3%–15.3% minority residents)	8.81
Lowest quartile (least minorities) (1.1%–5.3% minority residents)	12.37
Median family size	
Highest quartile (largest families) (median family size, 3.15–3.88 persons)	7.84
50%–75% quartile (median family size, 3.03–3.15 persons)	8.96
25%–50% quartile (median family size, 2.93–3.03 persons)	8.16
Lowest quartile (smallest families) (median family size, 2.49–2.93 persons)	11.77

Table 3
Univariate Analysis Results, Entire Cohort

Category	ERR (95% CI)	P Value
County size		
Metropolitan (>50,000 residents)	1.00	.07*
Micropolitan (>20,000 residents)	.99 (.81–1.22)	.96
Rural (<20,000 residents)	.82 (.68–.97)	.0225
Percent below poverty (continuous variable)		
10% increase	.84 (.76–.93)	.0007
Percent minority (continuous variable)		
1% increase	.997 (.94–1.001)	.09
Median family size (continuous variable)		
1 person increase	.77 (.55–1.06)	.10

* Overall P value (2 degree-of-freedom test).

Table 4
Multivariate Analysis Results, Entire Cohort

Category	ERR	P Value
County size		
Metropolitan (>50,000 residents)	1.00	.24*
Micropolitan (>20,000 residents)	1.03 (.83–1.26)	.80
Rural (<20,000 residents)	.87 (.72–1.03)	.11
Percent below poverty (continuous variable)		
10% increase	.86 (.77–.95)	.003

* Overall P value (2 degree-of-freedom test).

Family size and minority status were not associated with lower rates of transplantation in any model. Thus, the most important predictor of access to URD alloHCT was the poverty rate in the county of residence.

The lack of a significant difference in transplantation rates for pediatric patients in areas with higher poverty rates is an interesting finding. It is possible that this finding can be attributed to differences in statistical power, due to smaller numbers in that subgroup. Alternatively, barriers to transplantation (eg, insurance status, presence of a caregiver, clinical trial rates) are different in the pediatric and adult settings. This is an area that merits more study.

There are several reasons why patients living in areas with higher rates of poverty might have lower rates of transplantation. First, although Medicaid coverage is available to some families below the poverty line, Medicaid does not cover all direct and indirect costs of alloHCT. In addition, areas with higher rates of residents below the poverty line also have higher rates of poor residents but with income levels above the threshold required for Medicaid. Finally, there are a number of ancillary costs associated with transplantation that are not covered by insurance that might be a barrier to transplantation.

This study has several strengths and weaknesses. It is the only study reported to date reviewing access to alloHCT across different sociodemographic populations, using 2 well-established population-based registries (SEER and CIBMTR). Our results are consistent with previous studies in other fields, showing that poverty rate has a clear impact on transplantation rate.

This study was restricted to URD alloHCT only. Although we believe that this is a reasonable surrogate for transplantation activity in general, this hypothesis was not tested with this study. There are several reasons why rates of URD alloHCT might differ from overall transplantation rates, related primarily to donor availability. We attempted to address this by including average family size in the model. In all transplantation-related variables reviewed in the CIBMTR dataset, there were no other differences between the recipients of related donor and URD alloHCT. Finally, owing to the lower rates of

available matched URDs in other racial groups [1], we attempted to address differences in the availability of matched URDs through a sensitivity analysis restricted to white Americans. The primary conclusion of our study—lower transplantation rates in areas with more poverty—was upheld in this subgroup analysis. Thus, we believe that access to URD alloHCT is a reasonable surrogate for access to alloHCT in general.

In addition, there was a significant amount of missing ZIP code data (25%). While we believe these are missing at random, this is a weakness of our study. There was no difference in baseline transplantation-related variables between patients with available and missing ZIP code data, suggesting no significant bias as a result of this missing data.

It is a notable finding that only 10% of patients diagnosed with AML, ALL, and MDS went on to receive an allogeneic transplant from a URD. URD was the most common donor source throughout this study period, accounting for approximately 40% of all alloHCTs performed [12]. Given that large donor versus no donor studies done in that time period showed that the majority of patients with AML would benefit from allogeneic transplantation [15], this transplantation rate seems low. Reasons for the low overall rate of transplantation beyond sociodemographic barriers, including referring physician education and other systematic barriers to transplantation, should be studied.

We attempted to model the number of patients who might be excluded from transplantation owing to the aforementioned barriers. First, we assumed that the differences in transplantation rate seen in URD alloHCT were representative of all alloHCTs, regardless of donor source. Next, we modeled a scenario in which poverty as a barrier to transplantation was eliminated (setting the ERR for poverty to 1.0). Based on the transplantation activity reported to the CIBMTR, the total number of transplantations would increase by 2500 patients per year (an increase of approximately 30%).

In summary, we found that patients diagnosed with ALL, AML, and MDS from areas with higher poverty rates were less likely to receive an URD alloHCT. This effect was significant even when adjusting for other potential barriers, such as rural residency or racial origin. Modeling done using these results suggests that approximately 2500 patients annually do not undergo transplantation due to poverty. Given the significant number of patients annually who are potentially being excluded from transplantation due to socioeconomic status, attempting to improve access to transplantation in these populations should be a high priority for policy makers. Further studies are needed to advance our understanding of the specific factors driving lower access to transplantation in areas with lower socioeconomic status, and to determine which interventions might be successful in reducing this significant inequity.

Table 5
Univariate Sensitivity Analyses

County Attribute	Status	AML		Pediatric ALL		White Residents Only	
		Expected Rate	P Value	Expected Rate	P Value	Expected Rate	P Value
County size	Metropolitan	1.00	.01*	1.00	.25*	1.00	.04*
	Micropolitan	.91	.51	.73	.38	1.03	.80
	Rural	.71	.003	.70	.13	.79	.02
Percentage below poverty level	10% increase	.79	.0002	.80	.11	.85	.004
Percent minority	1% increase	.997	.21	.998	.73	1.002	.41
Family size	For each person increase	.995	.98	1.45	.26	.82	.27

* Overall P value (2 degree-of-freedom test).

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