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Association of Distance from Transplantation Center and Place of Residence on Outcomes after Allogeneic Hematopoietic Cell Transplantation

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A B S T R A C T

Regionalization of specialized health services can deliver high-quality care but may have an adverse impact on access and outcomes because of distance from the regional centers. In the case of hematopoietic cell transplantation (HCT), the effect of increased distance between the transplantation center and the rural/urban residence is unclear because of conflicting results from the existing studies. We examined the association between distance from primary residence to the transplantation center and rural versus urban residence with clinical outcomes after allogeneic HCT in a large cohort of patients. Overall mortality (OM), nonrelapse mortality (NRM), and relapse in all patients and those who survived for 200 days after HCT were assessed in 2849 patients who received their first allogeneic HCT between 2000 and 2010 at Fred Hutchinson Cancer Research Center (FHCRC)/Seattle Cancer Care Alliance. Median distance from FHCRC was 263 miles (range, 0 to 2740 miles) and 83% of patients were urban residents. The association between distance and the hazard of OM varied according to conditioning intensity: myeloablative (MA) versus nonmyeloablative (NMA). Among MA patients, there was no evidence of an increased risk of mortality with increased distance, but for NMA patients, the results did show a suggestion of increased risk of mortality for some distances, although globally the difference was not statistically significant. In the subgroup of patients who survived 200 days, there was no evidence that the risks of OM, relapse, or NRM were increased with increasing distance. We did not find any association between longer distance from transplantation center and urban/rural residence and outcomes after MA HCT. In patients undergoing NMA transplantations, this relationship and how it is influenced by factors such as age, payers, and comorbidities needs to be further investigated.

INTRODUCTION

Hematopoietic cell transplantation (HCT) is a commonly used modality for treatment of many hematological malignancies. Because of patient referral and selection patterns, many patients receive HCT at transplantation centers that are distant from their homes. The information about the association of geographic proximity to transplantation center and outcomes after HCT is conflicting. Although 1 study showed worse survival after 1 year for patients with $\geq$ 160 minutes driving time from the transplantation center, another study did not show an adverse impact of geographic distance from the transplantation center for patients living beyond 170 miles from transplantation center [1,2].

Another geographic parameter that may be important is rural versus urban residence, as most transplantation centers are in urban areas. Additionally, rural-urban residence may reflect differential socioeconomic parameters, such as income, education etc. Outcomes after autologous HCT have been shown to be worse for patients from rural areas. However, no significant differences in allogeneic HCT outcomes have been found between rural and urban residents in earlier studies that included patients who underwent transplantation before 2004 [3,4].

The purpose of this study was to examine the association between distance from primary residence to the transplantation center (for distances much larger than previously

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studied) and rural versus urban residence with major clinical outcomes after allogeneic HCT in a large cohort of patients.

PATIENTS AND METHODS

The study included 2849 patients who resided in the United States and received their first allogeneic transplantation between 2000 and 2010 at Fred Hutchinson Cancer Research Center (FHCRC)/Seattle Cancer Care Alliance. During the first 80 to 100 days after transplantation, patients reside within 30 minutes of the transplantation center. After this period, most are discharged to return home and resume care with their local hematologist-oncologists, unless current clinical condition requires continued care at the transplantation center. Most allogeneic HCT patients return to FHCRC/Seattle Cancer Care Alliance to be evaluated 1 year after HCT in a dedicated long-term follow-up (LTFU) clinic. Patients with chronic graft-versus-host disease (GVHD) may return sooner and continue to be seen by the LTFU clinic every 3 to 6 months [5]. These visits are encouraged but not mandated. Through use of telemedicine strategies, the LTFU program partners with local doctors to provide prompt consultations over the phone or in person for medical complications. In addition to providing clinical support for HCT survivors, the program also maintains a comprehensive database that includes annual contact with patients and their providers and status updates [6].

The study protocol was approved by the FHCRC institutional review board.

Variables

Demographic and clinical data including age, sex, race/ethnicity (white versus other), and disease and transplantation characteristics were obtained from the institutional database. Median income based on residence zip code was derived from census 2000 data (used as a proxy for patient socioeconomic status). *Place of residence* was defined using rural urban commuting area code and dichotomized into urban or rural designation. Urban areas consisted of urban commuting and urban core, whereas rural areas consisted of large rural commuting, large rural core, small rural commuting, and small rural core.

Outcomes

The outcomes considered were overall mortality (OM), nonrelapse mortality (NRM), and relapse. *NRM* was defined as death without a prior relapse. OM was calculated from time of transplantation to death, with death from any cause considered as an event. Surviving patients were censored at the time of last follow-up. Patients alive without relapse were censored at the time of last follow-up for the relapse endpoint.

Statistical Methods

Unadjusted estimates of overall survival were obtained from the method of Kaplan and Meier, whereas cumulative incidence estimates were used to summarize NRM and relapse. For these purposes, NRM was treated as a competing risk for relapse and relapse was treated as a competing risk for NRM. Cox regression models were used to assess the association between distance and the cause-specific hazards of failure for each endpoint as well as the difference in hazards between urban and rural dwelling. All regression models were adjusted for income, disease severity (low versus intermediate versus high), patient/donor cytomegalovirus serostatus, patient age at HCT, use of total body irradiation in conditioning, conditioning intensity, source of stem cells, type of donor (related versus unrelated), and year of HCT. Distance to transplantation center was modeled as a continuous (both linear and nonlinear) variable as well as a categorical variable with groups defined as 0 to 100 miles, 100 to 500 miles, 500 to 1000 miles, and $>$ 1000 miles from FHCRC. Overall mortality was also assessed by using an alternate categorical model with distance dichotomized at 170 miles as done in previous studies [1,2]. The nonlinear modeling of distance was performed using a 5-knot restricted cubic spline with knots at the 5th, 25th, 50th, 75th, and 95th percentiles of distance. Various interaction terms (eg, with conditioning intensity, urban versus rural dwelling, median income, age) were fit by modeling distance as a continuous linear variable. Because of the reduced power to detect a statistically significant interaction relative to a main effect, interaction tests resulting in a P value less than .15 were considered as worthy of separately examining relevant subgroups. Similar analyses were conducted among the subset of patients who survived to 200 days (a time by which most patients are discharged home). P values resulting from regression models were estimated using the Wald test, and no adjustments were made for multiple comparisons.

RESULTS

Clinical Characteristics of the Cohort

Median age of the 2849 study subjects was 47.4 (range, .4 to 78.9) years and 59% were males. Sixty-one percent of transplantations were done for myeloid diseases, 33% patients received nonmyeloablative (NMA) conditioning, and 49% had high-risk disease. Median follow-up from HCT among survivors was 7 years (range, 0 to 14 years). Median distance from FHCRC was 263 miles (range, 0 to 2740 miles) and 83% of study subjects were urban residents. The median estimated income was $60,618 (range, $11,713 to $205,243). Table 1 summarizes the sociodemographic-, disease-, and transplantation-related characteristics of patients, both overall and in groups defined in terms of distance from FHCRC.

Association between Distance, Urban Residence, and Outcomes among All Patients

There were a total of 1566 deaths, 744 NRM events, and 807 relapses during the follow-up period, contributing to estimated 5-year probabilities of 48% (95% confidence interval [CI], 46% to 50%) for overall survival, 30% (95% CI, 28% to 32%) for relapse, and 27% (95% CI, 25% to 28%) for NRM. A subset of patients (n = 219) who were conditioned with NMA regimens had insufficient follow-up information for relapse and, therefore, are not included in any analyses of NRM or relapse.

OM

There was a suggestion (interaction $P = .14$) that the association between distance and the hazard of mortality varied according to conditioning intensity (myeloablative [MA] versus NMA). Accordingly, models are fit separately for each of these conditioning groups (Table 2). The alternate categorical model did not show any evidence of an increased risk of OM for distances $>$ 170 miles compared with that for distances $<$ 170 miles (hazard ratio [HR], .88; 95% CI, .77 to

Table 1
Patient Characteristics

Characteristic	Distance of 0 to 100 Miles	Distance of 100 to 500 Miles	Distance of 500 to 1000 Miles	Distance > 1000 Miles
n	1063	542	219	1025
Age, median, yr	47.5	47.4	47.3	47.2
Income, median	62,962	47,828	64,144	65,682
NMA conditioning	36%	36%	36%	29%
Urban resident	91%	66%	75%	87%
Disease severity				
Low risk	31%	32%	36%	34%
Intermediate risk	19%	20%	19%	17%
High risk	51%	48%	45%	49%
CMV, patient/donor				
+/+	24%	22%	20%	25%
+/−	22%	23%	19%	26%
−/+	10%	8%	8%	9%
−/−	23%	30%	29%	27%
Unknown	20%	17%	24%	13%
TBI in prep	68%	63%	67%	59%
Source of stem cells				
BM	22%	23%	22%	21%
Cord	6%	5%	9%	4%
PBSC	72%	73%	69%	75%
URD	53%	53%	62%	58%
HCT 2000-2005	49%	55%	54%	69%
HCT 2006-2010	51%	45%	46%	31%
Follow-up, median, yr	6.07	6.27	6.43	8.2

CMV indicates cytomegalovirus; TBI, total body irradiation; BM, bone marrow; PBSC, peripheral blood stem cells; URD, unrelated donor.