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Hematopoietic Cell Transplantation in Young Adult Acute Lymphoblastic Leukemia: A United States Population-Level Analysis

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In this population-based evaluation of adolescents and young adults (AYA) acute lymphoblastic leukemia (ALL), we describe patterns of care (POC) and outcomes regarding hematopoietic cell transplantation (HCT) in first complete remission (CR1). Data were abstracted from the 2013 United States Surveillance, Epidemiology, and End Results POC study; newly diagnosed AYA ALL were included. Multivariable logistic regression evaluated associations with HCT in CR1; Cox proportional hazards regression evaluated survival associations. Of 399 AYAs with ALL included, 102 (28.5%) underwent HCT in CR1. High-risk cytogenetics (odds ratio [OR] = 4.86, 95% confidence interval [CI] = 3.02–7.83) and hyper-cyclophosphamide, vincristine, adriamycin, and dexamethasone (CVAD) induction (OR = 1.84, 95% CI = 1.07–3.16) were associated with HCT in CR1. Two-year cumulative incidence of relapse, relapse-free survival (RFS), and overall survival (OS) of the entire cohort were 28.3% (95% CI = 23.4–33.4), 69.3% (95% CI = 63.6–74.3%), and 84.1% (95% CI = 79.7–87.5), respectively. Two-year RFS was significantly higher in patients receiving CR1 HCT relative to chemotherapy (83.6%, 95% CI = 72.6–90.5% vs. 64.3%, 95% CI = 57.5–70.3), but no difference was seen in 2-year OS (88.9%, 95% CI = 80.8–93.7 vs. 82.5%, 95% CI = 77.2–86.7). Treatment at a nonteaching hospital was independently associated with inferior OS (hazard ratio = 2.15, 95% CI = 1.23–3.76). Although the ALL landscape is changing, these data provide a snapshot of the use and outcomes of HCT for AYA ALL across the United States.

Keywords: acute lymphoblastic leukemia, stem cell transplantation, adolescent and young adult, population sciences

Introduction

Adolescents and young adults (AYA) with acute lymphoblastic leukemia (ALL), defined by the National Cancer Institute (NCI) as individuals diagnosed between the ages of 15 and 39 years, represent a unique population caught between pediatric and adult cancer care. Emerging literature suggests that treatment decisions and AYA ALL outcomes are significantly influenced by location of ALL care.[1–4] For example, AYAs treated in the adult community cancer setting are more likely to receive the adult ALL regimen hyper-cyclophosphamide, vincristine, adriamycin, and dexamethasone (CVAD) than pediatric-inspired ALL regimens, whereas AYAs treated in the pediatric setting universally receive pediatric ALL protocols.[1,4] Furthermore, AYA ALL patients experience significantly superior survival when treated at NCI/Children's Oncology Group (COG) designated cancer centers, presumably as a result of increased experience and access to clinical trials and newer approaches available at these centers.[3,4]

The optimal use of hematopoietic cell transplantation (HCT) in AYA ALL has also been a subject of debate. In 2008, the largest prospective study evaluating HCT in adult ALL, MRC UKALLXII/ECOG E2993, reported that allogeneic HCT in first complete remission (CR1) was significantly superior to a traditional adult multiphase ALL

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chemotherapy consolidation regimen in younger adults (ages 18–35 years) with standard risk (SR) ALL features.[5] However, a survival advantage was not demonstrated after allogeneic HCT for adults >35 years or those with additional high-risk ALL features.[5] At approximately the same time as the trial's publication, reports were emerging that AYA ALL patients experience superior outcomes when treated following pediatric ALL regimens as opposed to traditional adult ALL chemotherapy regimens.[6–9] As a result, pediatric ALL regimens have been administered with increasing frequency for AYA ALL patients, although this approach is still not universally adopted by adult oncologists.[1,4] Allogeneic HCT has not been prospectively tested against pediatric ALL consolidation; however, a retrospective comparison suggested that the pediatric approach is superior with equivalent relapse rate and less treatment-related mortality.[10]

Although population-level data have described the frontline ALL regimens administered to AYA ALL patients across a variety of treatment settings in the United States,[1,4] the current use of allogeneic HCT as AYA ALL consolidation remains unknown. Despite the MRC UKALL-XII/ECOG E2993 conclusions that allogeneic HCT should be considered as consolidation for SR ALL in CR1, expert opinion remains divided on the optimal role for HCT in AYA ALL, leading many to conclude that the exposure to the risks of HCT is only warranted for AYAs with high-risk disease features.[11–13] Given the knowledge gaps related to the use of HCT in AYA ALL, we sought to describe patient, clinical, and treatment setting characteristics associated with the use of allogeneic HCT in CR1 among AYA ALL patients diagnosed across the United States, as well as outcomes associated with HCT and non-HCT approaches using the NCI Patterns of Care (POC) study.

Methods

NCI POC data and sampling methods

The NCI Surveillance, Epidemiology, and End Results (SEER) program is a population-based set of cancer registries that maintains information on incident cancer diagnoses arising within designated geographical areas, which cover ~28% of the United States population.[14] The SEER program routinely collects information on cancer diagnosis, stage, initial course of treatment, and patient demographics. However, because SEER data collection is primarily hospital based, therapy administered in outpatient settings may be underreported. Therefore, each year, the NCI conducts a POC study to obtain more complete information on cancer therapies for selected cancers. For the POC studies, SEER patients are stratified by cancer site, age, race/ethnicity, and registry, and random sampling is performed from each stratum. Non-Hispanic (NH) blacks, Hispanics, Asians/Pacific Islanders, and American Indians/Alaskan Natives are oversampled to obtain more stable estimates. Medical records from both inpatient and outpatient encounters are reviewed for tumor, treatment, and comorbidity information. In addition, treating physicians are contacted to verify treatments administered and to identify other treating physicians for query. Information regarding physician specialty and treating facilities are also recorded. The NCI POC studies receive Institutional Review Board approval as required by the registries.

Patient sample

The current analysis utilized the NCI POC study of AYA cancer patients (15–39 years) diagnosed from January 1, 2012 to December 31, 2013 and registered in the population-based SEER program. We included 399 AYAs with first primary ALL (International Classification of Diseases for Oncology, 3rd edition morphology codes 9811–9818, 9827, 9835–9837). Patients were excluded from the study if they had a previous history of cancer other than nonmelanoma skin cancer, were diagnosed with another cancer simultaneously, or were diagnosed by autopsy or death certificate only. Patients who had relapse/progression within 3 months of diagnosis ($n = 14$) or died within 3 months of diagnosis ($n = 18$) were excluded from analyses examining factors associated with HCT in CR1, given that these patients would not clearly have been eligible for a first remission transplant; these patients were included in survival analyses.

Study measures

From the study data set, patients were classified as having allogeneic HCT in CR1 if the HCT occurred without relapse/progression before the HCT date. Patients who underwent HCT at any time after relapse or progression were not considered to have undergone HCT in CR1. In addition, data were obtained regarding the presence of high-risk ALL cytogenetic abnormalities including Philadelphia chromosome, mixed lineage leukemia translocation, hypodiploid, intrachromosomal amplification of chromosome 21 (iAMP21), induction therapy administered, and central nervous system involvement at diagnosis. High-risk ALL was defined as the presence of any high-risk cytogenetics; molecular subtypes and white blood cell count at diagnosis were not available. Induction therapy was classified as asparaginase-containing, hyper-CVAD, and other or unknown. Comorbidity classification was reported based on previously developed methodology and categorized as yes/no.[15] Specifically, we identified individuals as having a comorbidity if they had medical record-based evidence of asthma, cardiovascular events, cerebral vascular events, diabetes, endocrine disorders, gastrointestinal disorders, HIV/AIDS, hematologic disorders, hypertension, liver disorders, life-threatening infections, mental health disorders, neurologic disorders, obesity, renal disorders, or rheumatologic/autoimmune disorders.[15]

We used the original SEER record to obtain the date of diagnosis, registry site, age at diagnosis, sex, race/ethnicity (NH white, NH black, Hispanic, NH Asian, other/unknown), health insurance at diagnosis (private, public, no insurance/unknown), census tract median income, histology (B or T cell), and date of death. Physician specialty (adult hematology oncology, pediatric oncology, and other/unknown) and treating facility characteristics (number of beds and residency training program) were obtained from the POC study data. Teaching hospitals were defined as those with residency training programs and large hospitals were considered those with >400 beds.

Statistical analyses

Descriptive statistics characterized the study population. Chi-squared tests were used to assess patient, clinical, and treating facility characteristics associated with HCT in CR1. To evaluate the associations with receipt of HCT in CR1, we used logistic regression to calculate odds ratios (ORs) and associated 95% confidence intervals (CIs). Multicollinearity was assessed by examining variance inflation factors (VIF). All models met our criteria of nonmulticollinearity with VIF <10. Additional models evaluating young adults (20–39 years; excluding adolescents) were examined.

Using nonparametric methods accounting for the competing risk of death,[16] we calculated the cumulative incidence of ALL relapse for all patients and by HCT in CR1 at 1 and 2 years from cancer diagnosis. Gray's K-sample test was used to determine whether cumulative incidence of ALL relapse differed by HCT in CR1.[17] We also computed Kaplan–Meier survival curves for relapse-free survival (RFS) and overall survival (OS), with the log-rank test used to compare the survival distributions by HCT in CR1. For RFS, we measured survival time in months from ALL diagnosis to date of first relapse, the study cutoff date (1 and 2 years), the date of death, or the date of last known contact, whichever occurred first. For OS, we measured survival time in months from ALL diagnosis to the study cutoff date (1 and 2 years), the date of death, or the date of last known contact, whichever occurred first.

To further evaluate associations with the risk of death from all causes, we used Cox proportional hazards regression to calculate hazard ratios (HRs) and associated 95% CIs. For deceased patients, we measured survival time in months from the date of diagnosis to the date of death. Patients alive at the study end date (December 31, 2015) were censored at this time or at the date of last known contact, whichever occurred earlier. Multivariable regression models included variables significantly associated with the outcome in univariate models (e.g., age, health insurance, ALL cytogenetic risk, and physician specialty) or with *a priori* hypotheses for inclusion (e.g., sex, race/ethnicity, ALL histology, treating facility setting, and ALL induction regimens). Effect modification was assessed between HCT and patient, clinical, and treating facility characteristics by including interaction terms in the multivariable Cox regression models. In all Cox regression models, the proportional hazards assumption was assessed numerically based on cumulative sums of Martingale residuals and visually based on inspection of the survival curves [log (–log) of the survival distribution function by log (months)]; variables found to violate this assumption were included as a stratifying variable to allow for differing baseline hazards. HCT in CR1 was considered a time-dependent variable. Analyses were weighted to reflect the SEER populations. Analyses were performed using SAS® (9.4) and $p < 0.05$ was considered statistically significant.

Results

AYA ALL patient characteristics

The median age of AYA ALL patients in our study was 24 years (interquartile range, 18–32 years). Patients were predominantly men (70.4%) and Hispanic (48.8%) with private insurance (55.0%) (Table 1). The majority (84.9%) had B cell as opposed to T cell ALL, and 73.0% were considered to have an SR ALL cytogenetic profile. Almost two-thirds of AYAs were treated by adult hematology oncology providers, whereas one-third were treated by pediatric oncologists. Most patients were treated at large (47.6%) or small/medium (38.4%) size teaching hospitals. Fifty-eight percent received an asparaginase-containing ALL induction regimen, whereas 31.7% received hyper-CVAD, and 10.4% received another or unknown induction regimen.

HCT utilization in CR1

A total of 102 eligible AYAs (28.5%) underwent allogeneic HCT in CR1. Characteristics significantly associated with receipt of HCT in CR1 in univariate analysis (Table 2) included older age category at diagnosis, private (vs. public/no/unknown) health insurance, high-risk cytogenetics, adult hematology oncology (vs. pediatric oncology) provider specialty, and hyper-CVAD (vs. asparaginase-containing) induction regimen. In multivariate analysis (Table 3), high-risk cytogenetics and receipt of hyper-CVAD induction regimen (vs. asparaginase containing, $p = 0.027$) remained significantly associated with increased odds of allogeneic HCT in CR1, whereas care in a nonteaching hospital was significantly associated with lower odds of allogeneic HCT in CR1 (vs. large teaching, $p = 0.021$). When multivariate analyses were limited to AYAs 20–39 years, high-risk cytogenetics ($p < 0.001$), adult hematology oncology provider specialty ($p = 0.007$) were significantly associated with higher odds of allogeneic HCT in CR1; hyper-CVAD induction demonstrated a borderline association (vs. asparaginase containing, $p = 0.057$) (Supplementary Table S1).

AYA ALL outcomes and predictive models of OS

The median follow-up time of AYA ALL patients in our study was 19 months and range was 0–35 months. Cumulative incidence of relapse, RFS, and OS are detailed in Table 4. Two-year cumulative incidence of relapse was significantly lower in patients receiving HCT in CR1 as opposed to those not receiving HCT in CR1 (15.1%; 95% CI = 8.1–24.1 vs. 32.8%; 95% CI = 26.9–38.9). This translated into a significant improvement in 2-year RFS (83.6%; 95% CI = 72.6–90.5 vs. 64.3%, 95% CI = 57.5–70.3), but no statistically significant differences in 2-year OS (88.9%, 95% CI = 80.8–93.7 vs. 82.5%, 95% CI = 77.2–86.7).

In multivariate analysis examining covariates associated with OS in AYAs with ALL (Table 5) and in AYAs aged 20–39 years (Supplementary Table S2), care in a nonteaching hospital (vs. large teaching hospital) (HR = 2.15, 95% CI = 1.23–3.76), and other/unknown induction regimen (vs. asparaginase containing) (HR = 8.76, 95% CI = 4.66–16.48) were associated with inferior OS. Receipt of HCT in CR1 was not significantly associated with OS in multivariate analysis, although there was a trend toward inferior OS in the entire AYA cohort (HR = 1.88, 95% CI = 0.99–3.56), but not in the model limited to AYAs 20–39 years (HR = 1.26, 95% CI = 0.62–2.55). Among all AYAs, sensitivity analyses evaluating the role of HCT in CR1 on OS excluding the 32 patients with relapse/progression or death within 3 months of diagnoses similarly demonstrated no

Table 1. Patient, Clinical, and Treating Facility Characteristics of Adolescents and Young Adults Diagnosed with Acute Lymphoblastic Leukemia, Stratified by Allogeneic Hematopoietic Cell Transplantation in First Complete Remission, 2012–2013

	Total	*HCT in CR1*	*No HCT in CR1*	
Characteristic	n *(Wt %)*	n *(Wt %)*	n *(Wt %)*	p-*Value*
Total	399 (100.0)	102 (100.0)	297 (100.0)	
Location of diagnosis[a]				
East	80 (18.4)	21 (18.8)	59 (18.3)	
Mid-southwestern	58 (12.9)	18 (17.5)	40 (11.2)	
West	261 (68.7)	63 (63.7)	198 (70.5)	0.546
Age of diagnosis, years				
15–19	124 (33.1)	19 (20.4)	105 (37.6)	
20–24	82 (21.1)	18 (16.9)	64 (22.6)	
25–29	74 (17.7)	20 (21.6)	54 (16.3)	
30–34	57 (14.5)	20 (19.9)	37 (12.5)	
35–39	62 (13.6)	25 (21.1)	37 (10.9)	0.002
Sex				
Male	275 (70.4)	69 (68.0)	206 (71.2)	
Female	124 (29.6)	33 (32.0)	91 (28.8)	0.747
Race/ethnicity				
NH white	153 (39.0)	48 (47.9)	105 (35.8)	
NH African American	22 (5.2)	<6	18 (5.8)	
Hispanic	193 (48.8)	39 (38.8)	154 (52.4)	
Other	31 (7.0)	>9	20 (5.9)	0.049
Health insurance				
Private	215 (55.0)	67 (66.6)	148 (50.9)	
Public	169 (41.3)	>29	136 (44.9)	
No insurance/unknown	15 (3.7)	<6	13 (4.2)	0.019
Income[b]				
<55	39 (11.0)	7 (7.9)	32 (12.0)	
55 to <75	231 (56.9)	62 (62.1)	169 (55.1)	
>75	129 (32.1)	33 (30.0)	96 (32.9)	0.019
Comorbidities				
No	225 (58.7)	53 (52)	172 (61.1)	
Yes	174 (41.3)	49 (48)	125 (38.9)	0.296
ALL histology				
B cell	340 (84.9)	91 (87.6)	249 (83.9)	
T cell	59 (15.1)	11 (12.4)	48 (16.1)	0.187
ALL cytogenetic risk				
Standard risk	291 (73.0)	49 (48.4)	242 (81.8)	
High risk	108 (27.0)	53 (51.6)	55 (18.2)	<0.001
Philadelphia chromosome	70 (17.0)	40 (39.1)	30 (9.1)	
MLL translocations	23 (5.1)	8 (7.0)	15 (4.5)	
Hypodiploidy	10 (2.6)	<6	<6	
Intrachromosomal amplification	18 (5.0)	<6	>9	
CNS involvement at diagnosis				
No	342 (85.9)	90 (88.6)	252 (84.9)	
Yes	46 (11.2)	>9	35 (11.6)	
Unknown	11 (2.9)	<6	10 (3.5)	0.420
Treating physician specialty				
Pediatric oncology	122 (33.3)	>19	102 (37.6)	
Adult hematology oncology	271 (65.1)	81 (77.7)	190 (60.6)	
Other/unknown	6 (1.6)	<6	<6	0.016
Treating facility setting				
Large teaching hospital	192 (47.6)	54 (51.4)	138 (46.2)	
Nonteaching hospital	61 (14.1)	11 (10.1)	50 (15.5)	
Small/medium teaching hospital	146 (38.4)	37 (38.5)	109 (38.3)	0.289
ALL induction regimen				
Asparaginase containing	230 (57.8)	49 (47.1)	181 (61.7)	
Hyper-CVAD	131 (31.7)	52 (51.2)	79 (24.8)	
Other	18 (5.9)	<6	17 (7.4)	
Unknown	20 (4.5)	<6	20 (6.1)	<0.001

[a]East: Atlanta (Metropolitan), Connecticut, New Jersey, Kentucky, Louisiana; Mid-Southwest: Detroit (Metropolitan), Iowa, Utah, New Mexico; West: San Francisco (Oakland), San Jose-Monterey, Seattle (Puget Sound), Hawaii, Los Angeles, California other.
[b]Census tract medium family income, in thousands of dollars.

Wt, weighted; NH, non-Hispanic; CNS, central nervous system; MLL, mixed lineage leukemia; ALL, acute lymphoblastic leukemia; HCT, hematopoietic cell transplantation; CR1, first complete remission; CVAD, cyclophosphamide, vincristine, adriamycin, and dexamethasone.

Table 2. Unadjusted Odds Ratios and Associated 95% Confidence Intervals for the Association of Clinical and Treating Facility Characteristics with Allogeneic Hematopoietic Cell Transplantation in First Complete Remission Among Adolescents and Young Adults Diagnosed with Acute Lymphoblastic Leukemia, 2012–2013

Characteristics	*OR (95% CI)*	p-*value*
Location[a]		
West	Reference	
East	1.02 (0.62–1.68)	
Mid-southwest	1.72 (0.99–2.97)	0.146
Age at diagnosis, years		
15–19	Reference	
20–24	1.44 (0.79–2.60)	
25–29	3.03 (1.68–5.48)	
30–34	3.21 (1.75–5.90)	
35–39	4.03 (2.18–7.45)	<0.001
Sex		
Male	Reference	
Female	1.18 (0.78–1.79)	0.422
Race/ethnicity		
NH white	Reference	
Hispanic	0.60 (0.40–0.91)	
NH black	0.47 (0.17–1.30)	
Other	1.38 (0.67–2.86)	0.024
Heath insurance		
Private	Reference	
Public/no/unknown	0.51 (0.34–0.76)	<0.001
Income[b]		
<55	Reference	
55–75	1.71 (0.85–3.42)	
≥75	1.30 (0.62–2.71)	0.201
Comorbidities		
No	Reference	
Yes	1.59 (1.08–2.34)	0.019
ALL histology		
B cell	Reference	
T cell	0.73 (0.42–1.29)	0.283
ALL cytogenetic risk		
Standard risk		
High risk	4.75 (3.13–7.21)	<0.001
CNS involvement		
No	Reference	
Yes	0.81 (0.43–1.50)	0.454
Physician specialty		
Pediatric oncology	Reference	
Adult hematology oncology	2.61 (1.68–4.05)	<0.001
Treating facility		
Large teaching hospital	Reference	
Nonteaching hospital	0.59 (0.31–1.11)	
Small teaching hospital	0.81 (0.54–1.23)	0.229
Induction regimen		
Asparaginase containing	Reference	
Hyper-CVAD	2.86 (1.91–4.29)	
Other/unknown	0.25 (0.07–0.92)	<0.001

Analyses exclude 32 patients who had relapse/progression or died within 3 months of diagnosis.

[a]East: Atlanta (Metropolitan), Connecticut, New Jersey, Kentucky, Louisiana; Mid-southwest: Detroit (Metropolitan), Iowa, Utah, New Mexico; West: San Francisco (Oakland), San Jose-Monterey, Seattle (Puget Sound), Hawaii, Los Angeles, California other.

[b]Census tract medium family income, in thousands of dollars.

OR, odds ratio; CI, confidence interval.

Table 3. Multivariable-Adjusted Odds Ratios and Associated 95% Confidence Intervals for the Association of Patient, Clinical, and Treating Facility Characteristics with Allogeneic Hematopoietic Cell Transplantation in First Complete Remission Among Adolescents and Young Adults Diagnosed with Acute Lymphoblastic Leukemia, 2012–2013

Characteristic	*OR (95% CI)*	p-*Value*
Age at diagnosis, years		
15–19	Reference	
20–24	1.21 (0.56–2.61)	
25–29	1.92 (0.82–4.51)	
30–34	1.69 (0.72–3.99)	
35–39	2.76 (1.11–6.90)	0.177
Sex		
Male	Reference	
Female	0.72 (0.44–1.18)	0.190
Race/ethnicity		
NH white	Reference	
Hispanic	0.93 (0.55–1.55)	
NH black	0.52 (0.17–1.61)	
Other	1.98 (0.83–4.71)	0.225
Heath insurance		
Private	Reference	
Public/no/unknown	0.67 (0.41–1.09)	0.105
ALL cytogenetic risk		
Standard risk	Reference	
High risk	4.86 (3.02–7.83)	<0.001
Physician specialty		
Pediatric oncology	Reference	
Adult hematology oncology	1.79 (0.87–3.66)	0.113
Treating facility		
Large teaching hospital	Reference	
Nonteaching hospital	0.42 (0.20–0.88)	
Small teaching hospital	1.02 (0.63–1.65)	0.052
Induction regimen		
Asparaginase containing	Reference	
Hyper-CVAD	1.84 (1.07–3.16)	
Other/unknown	0.23 (0.06–0.92)	0.004

Adjusted for all variables in the table; analysis excludes 32 patients who had relapse/progression or died within 3 months of diagnosis.

significant association between HCT in CR1 and OS (HR = 1.51, 95% CI = 0.76–3.00, $p = 0.244$). We were unable to uncover any statistically significant interactions between HCT and other covariates.

Discussion

In our population-level study of patterns of HCT utilization in AYAs with ALL across the United States, we found that approximately one-quarter of AYA ALL patients are undergoing allogeneic HCT in CR1, and that high-risk ALL cytogenetics, and the receipt of nonasparaginase-containing induction regimens are independently associated with consolidative HCT. Despite randomized clinical trial results in young adult ALL demonstrating superiority of allogeneic HCT in CR1 for SR ALL,[5] these findings suggest that, in practice, allogeneic HCT is reserved for higher risk AYA ALL patients. Furthermore, the finding that HCT is significantly

Table 4. Association of Allogeneic Hematopoietic Cell Transplantation in First Complete Remission with Relapse, Relapse-Free Survival, and Overall Survival at 1 and 2 Years Among Adolescents and Young Adults Diagnosed with Acute Lymphoblastic Leukemia, 2012–2013

	Relapse	*RFS* % (95% CI)	*OS*
Total cohort			
1-Year	16.4 (12.9–20.4)	82.1 (77.7–85.8)	87.4 (83.6–90.3)
2-Year	28.3 (23.4–33.4)	69.3 (63.6–74.3)	84.1 (79.7–87.5)
HCT in CR1			
1-Year	10.2 (5.2–17.1)	87.8 (79.1–93.1)	88.9 (80.8–93.7)
2-Year	15.1 (8.1–24.1)	83.6 (72.6–90.5)	88.9 (80.8–93.7)
No HCT in CR1			
1-Year	18.7 (14.3–23.5)	79.5 (74.1–84.0)	86.9 (82.4–90.4)
2-Year	32.8 (26.9–38.9)	64.3 (57.5–70.3)	82.5 (77.2–86.7)

RFS, relapse-free survival; OS, overall survival.

associated with receipt of nonasparaginase-containing ALL regimens suggests that HCT is applied more often following adult ALL inductions rather than pediatric-inspired ALL protocols, which universally incorporate asparaginase.[18]

Based on our previous work demonstrating that AYA ALL therapies vary according to ALL treatment setting,[1,4] we hypothesized that use of consolidative allogeneic HCT would also differ across treatment settings. In this analysis, we confirm that almost two-thirds of AYAs with newly diagnosed ALL are treated in the adult cancer setting, whereas only one-third receive care from pediatric oncologists. As anticipated, ALL care delivered by an adult oncologist was associated with a doubling of the likelihood of HCT in CR1. Although we were unable to distinguish NCI/COG cancer centers from community centers in this study, we found that AYAs treated at nonteaching hospitals were significantly less likely to undergo HCT in CR1, and to have significantly inferior OS relative to AYAs treated at large teaching centers.

The unadjusted outcomes of our study population demonstrate that 2-year cumulative incidence of relapse and RFS are significantly superior following HCT in CR1; however, this did not translate into an OS benefit. This is likely because of the increase in nonrelapse mortality associated with HCT and mirrors the findings of other studies in this population demonstrating that ALL disease control is likely superior with HCT but this advantage is offset by the associated toxicities of transplantation.[10] As such, our multivariate analysis for OS did not demonstrate a significant benefit for HCT in CR1 overall (and if anything showed a nonsignificant trend toward inferior OS); however, our cohort size limited our ability to identify subgroups of ALL patients who may potentially benefit from HCT in CR1.

The optimal upfront management of AYA ALL remains controversial despite numerous prospective trial results and meta-analyses demonstrating favorable outcomes following pediatric ALL regimens, which universally incorporate asparaginase.[7,9,18–21] In our AYA ALL cohort drawn from a representative United States sample, we found that 43% of AYAs receive nonasparaginase-containing induction regimens, the majority of whom receive hyper-CVAD. Although these patients are more likely to receive allogeneic HCT in CR1, there seemed to be no significant difference in survival based upon receipt of asparaginase versus nonasparaginase-containing regimens. It is possible that the increased use of

Table 5. Multivariable-Adjusted Hazard Ratios and 95% Confidence Intervals for the Association Between Patient, Clinical, and Treating Facility Characteristics with Overall Survival Among Adolescents and Young Adults Diagnosed with Acute Lymphoblastic Leukemia, 2012–2013

Characteristic	*HR (95% CI)*	p-*Value*
Age at diagnosis, years		
15–19	Reference	
20–24	1.46 (0.63–3.38)	
25–29	2.56 (1.15–5.73)	
30–34	2.22 (0.95–5.20)	
35–39	2.24 (0.91–5.50)	0.162
Sex		
Male	Reference	
Female	1.06 (0.65–1.73)	0.801
Race/ethnicity		
NH white	Reference	
Hispanic	1.23 (0.73–2.09)	
NH African American	1.60 (0.61–4.20)	
Other	0.59 (0.22–1.63)	0.393
Heath insurance		
Private	Reference	
Public/no/unknown	1.30 (0.80–2.10)	0.293
ALL cytogenetic risk		
Standard risk	Reference	
High risk	1.68 (1.00–2.82)	0.051
Physician specialty		
Pediatric oncology	Reference	
Adult hematology oncology	1.65 (0.81–3.34)	0.165
Treating facility		
Large teaching hospital	Reference	
Nonteaching hospital	2.15 (1.23–3.76)	
Small/medium teaching hospital	0.81 (0.46–1.43)	0.007
Induction regimen		
Asparaginase containing	Reference	
Hyper-CVAD	1.41 (0.78–2.57)	
Other/unknown	8.76 (4.66–16.48)	<0.001
HCT in CR1		
No	Reference	
Yes	1.88 (0.99–3.56)	0.052

Adjusted for all variables in the table; HCT in CR1 was considered as time-dependent variable.

HCT in AYAs receiving nonasparaginase ALL regimens augmented survival of these patients such that outcomes for asparaginase and nonasparaginase-treated patients were equivocal.

Our work aims to provide a population-level snapshot of HCT utilization in AYA ALL across the United States using data abstracted for the 2013 SEER POC study. Although HCT utilization and outcomes data are available through other sources, such as the Center for International Blood and Marrow Transplantation Research, our analyses are unique in providing detailed population-level data in both transplanted and nontransplanted AYAs. However, as is inherent to population sciences research, we were limited by the data elements included in the POC data. Of note, we were unable to distinguish asparaginase-containing pediatric ALL regimens from adult ALL regimens, which would have enabled us to draw important comparisons. Previous work using population-level data has demonstrated that hyper-CVAD remains the most common adult ALL regimen used in the United States[1,4]; therefore, we suspect that a large proportion of the asparaginase group in this study were likely to have received pediatric or pediatric-inspired ALL protocols. Important disease-related variables such as molecular ALL subtypes and minimal residual disease status were unavailable, as were more discriminative information on treatment setting, such as NCI/COG status. Of interest, certain high-risk AYAs did not undergo HCT; additional research utilizing data sets that include additional variables of interest, such as minimal residual disease (MRD), would help delineate whether this finding may be a result of information that we could not characterize, such as MRD status, or perhaps a health disparity related to access to care. Furthermore, with a median follow-up of surviving patients of 19 months, we were unable to report long-term ALL outcomes of this population. Additional follow-up will be necessary to determine long-term outcomes associated with HCT versus non-HCT approaches in AYA ALL across the population.

The landscape of ALL therapy is changing dramatically with the incorporation of antigen-targeting therapies earlier in the course and for MRD clearance. Furthermore, as therapies evolve and salvage therapies for relapsed disease improve, referrals for HCT in CR1 may become less frequent because of the perception that HCT may be reserved for CR2. The role of HCT in ALL is likely to change further as chimeric antigen receptor T cell therapies are increasingly administered with curative intent. Although our current analysis incorporates data from earlier in this decade before the routine use of novel-targeted immunotherapies, it stands alone as a useful population-based ''real-world'' assessment of patterns of HCT use in AYA ALL that has not been previously described. Our findings confirm that contrary to prospective clinical trial results, HCT is less commonly utilized in SR ALL than in high-risk ALL, and more commonly applied as consolidation for AYAs receiving nonasparaginase-containing ALL regimens. Although the management of ALL is currently in evolution, these data provide an important snapshot of HCT for AYA ALL in the United States.

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Author Disclosure Statement

No competing financial interests exist.

Supplementary Material

Supplementary Table S1
Supplementary Table S2

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