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Effect of Stem Cell Transplant on Survival in Adult Patients With Acute Lymphoblastic Leukemia: NCDB Analysis

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Abstract. *Background: A retrospective analysis was performed to investigate the survival outcomes in adult acute lymphoblastic leukemia (ALL) based on treatment received. Materials and Methods: Data from 17,504 men and women (≥18 years of age) registered in the National Cancer Database who were diagnosed with ALL between 2004 and 2013 and had follow-up to the end of 2014, were analyzed. The primary predictor variable was treatment received, and overall survival was the outcome variable. Additional variables addressed and adjusted included gender, age, race, Charleston Comorbidity Index, level of education, income, insurance, distance traveled, facility type and diagnosing/treating facility. Results: The mean age of patients was 48.8 years with a standard deviation of 19.3 years. In multivariate analysis, after adjusting for secondary predictor variables, treatment modality was a statistically significant predictor of overall survival from ALL. Relative to patients who were treated with chemotherapy only, the patients who got chemotherapy and stem cell transplant had a decreased risk of mortality by 39%. Of the 5,409 patients between the ages of 18 and 39 years i.e. adolescent and young adults (AYA), no statistically significant survival difference was found between patients treated with stem cell transplant and those not. Conclusion: Stem cell transplant led to improved survival for all age groups except the AYA.*

Acute lymphoblastic leukemia (ALL) is characterized by clonal proliferation of lymphoblasts in bone marrow, blood, and other organs (1). The American Cancer Society estimated 5,970 new cases and 1,440 deaths from ALL in 2017 (2). ALL is the most common type of childhood leukemia and represents approximately 80% of acute leukemias in this age group. In contrast, ALL represents only 20% of acute leukemias in adults (1, 3). There have been recent advances in the understanding of molecular genetics, pathogenesis and newer targeted therapies for ALL. This has led to improvement in survival outcomes (4). Historically, survival in older adolescents and young adults (AYA) has been poor, with 5-year overall survival of approximately 40% (5-7), unlike children in whom the overall survival approaches 80% (8, 9). Older adults with ALL have the worst 5-year overall survival of approximately 24% for those aged 40-59 years and about a 17% for those aged 60-69 years (10). Molecular and cytogenetic heterogeneity in disease, patient-related factors (such as age, comorbidities, stage of illness and other socio-economic factors), and therapeutic approach are some factors that might explain the difference in survival outcomes (11-13). In recent years with improving research in the field of ALL and use of pediatric-inspired regimens, the overall survival for AYA with ALL has tremendously improved (14, 15).

The emergence of targeted therapies such as tyrosine kinase inhibitors (16) for Philadelphia (Ph.) +ALL, monoclonal antibodies to CD20 (17), nelarabine (18), blinatumomab (19) , and inotuzumab ozogamycin (20), represents a significant advancement and has led to improved outcomes in ALL. Previous studies of Ph+ ALL have shown improvement in overall survival with use of allogeneic SCT (21). Even in Ph- ALL with high-risk features, allogeneic stem cell transplant (SCT) has improved outcomes (22). With improving outcomes for AYA patients with the use of pediatric-inspired regimens and the advent of newer targeted treatments the utility of allo-transplant has been questioned. A retrospective analysis was carried out on adult patients with ALL registered in the National Cancer Database (NCDB) to investigate the survival outcomes of ALL based on treatment received.

Materials and Methods

The NCDB is a hospital-based cancer registry that is jointly maintained by the American College of Surgeons and the American Cancer Society. The NCDB captures approximately 70% of all newly diagnosed cases of cancer in the United States. The database

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standardizes data elements for patient demographics, tumor characteristics including stage and site-specific variables, zip-code level socioeconomic factors, facility characteristics and insurance status as well as treatments status. Patients diagnosed with ALL from 2004-2013 and followed-up to the end of 2014 between the ages of 18 and 90 years were included in the analysis. Descriptive data were gathered and further subdivided by treatment modality for the following characteristics: Gender, age, race, comorbidity score, year of diagnosis, payer status, income, education, distance from treating facility, facility type, delay in treatment and type of treatment. Age was divided into three sub-categories: 18-39 (AYA), 40-64 and 65-90 years. Race was aggregated into White, Black and Asian. The year of diagnosis was divided into 2004-2009 and 2010-2013. Payer status was categorized as uninsured, private, Medicaid or Medicare. Median household income at zip-code level was grouped as <$36 k and ≥$36 k. The percentage of adults in the patient's zip code which did not graduate from high school, as a measure of education, was grouped as <20% and ≥20%. Zip-code level of income and education were determined using 2000 census data. The distance from the patient's residential zip code to a medical center was grouped as <30 and ≥30 miles. Charlson Comorbidity Index, a score that indicates the overall health status of a patient, was defined as 0 or ≥1 (23). Facilities were classified by the NCDB into community cancer program, comprehensive community cancer centers, academic centers and integrated network cancer program. Treatment modality was grouped as chemotherapy only and chemotherapy with SCT.

Statistical analysis. Descriptive analysis was carried out on adult patients with ALL registered in NCDB to describe the age, gender, race, comorbidity index, year of diagnosis, insurance status, income, education distance traveled to their treatment center, facility type, class of care, treatment delay and type of treatment received. Multivariate Cox regression was used to assess the effect of treatment modalities on the survival of ALL adjusted for factors investigated in this study. Direct adjusted median overall survival was estimated by using multivariate Cox regression. Statistical analyses were performed with statistical software SAS 9.4 (SAS Institute Inc, Cary, NC, USA).

Results

Table I presents the patient characteristics of the patients with ALL in this study. There were 17,504 patients diagnosed with ALL between ages 18-90 years from the NCDB. Fifty-six percent were males. Approximately, 35% were AYA, 41% were between 40-64 years, and 24% were 65 years old or older. About 79% had a comorbidity index of zero. Approximately 55% of the patients were diagnosed between 2004 and 2009 and the rest were diagnosed between 2010 and 2013. About 32% had an annual income of less than $32 k. Seventy percent of the patients traveled less than 30 miles to reach their treatment center, and treatment started within 11 days of diagnosis in 80%. Eighty-four percent of patients received chemotherapy only. Only 13.9% of the patients received chemotherapy as well as SCT. Most patients were white males (87%), with no comorbidities (78%), and private insurance (49%).

Table I. *Patient characteristic (all ages).*

Factor	n	%
Gender		
Male	9864	56.35
Female	7640	43.65
Age, years		
18-39	6115	34.93
40-64	7138	40.78
≥65	4251	24.29
Race		
White	15081	87.24
Black	1490	8.62
Asian	715	4.14
Comorbidity		
0	13804	78.86
≥1	3700	21.14
Year of diagnosis		
2004-2009	8741	55.81
2010-2013	6922	44.19
Insurance		
Uninsured	1247	7.47
Private	8236	49.36
Medicaid	2645	15.85
Medicare	4558	27.32
Income		
<$36 k	5321	31.94
≥$36 k	11339	68.06
Education		
<20%	7360	44.19
≥20%	9294	55.81
Distance travelled		
<30 Miles	11843	69.37
≥30 Miles	5230	30.63
Diagnosis and treatment		
Same facility	9333	53.32
Different facility	8171	46.68
Treatment delay, days		
0-11	12255	80.77
≥12	2918	19.23
Treatment		
Chemotherapy only	15071	86.1
Chemotherapy + SCT	2433	13.9

SCT: Stem cell transplantation.

Table II presents the multivariate Cox regression analysis to calculate the hazards ratio of death. Gender, race, distance traveled to the treatment center, and facility type did not affect overall survival. Age and comorbidity index were found to significantly affect survival for ALL. Patients aged 40-64 years and 65 years or older were approximately two and three times, respectively, more likely to die compared to the AYA group. Patients with a co-morbidity index of 1 or more were 34% more likely to die compared to those with no comorbidity. The year of diagnosis also affected survival. Patients who were diagnosed 2010-2013 were 17% less likely to die compared to patients diagnosed earlier.

Table II. *Multivariate Cox regression, hazard ratio of death by factors (all ages).*

Factor	HR	95% CI		*p*-Value
		Lower	Upper	
Gender				
Male	1.00			
Female	1.032	0.984	1.082	0.20
Age, years				
18-39	1.00			
40-64	1.856	1.747	1.973	<0.00001
≥65	2.767	2.526	3.032	<0.00001
Race				
White	1.00			
Asian	0.882	0.777	1.002	0.05
Black	1.015	0.934	1.104	0.71
Comorbidity				
0	1.00			
1	1.339	1.267	1.415	<0.00001
Year of diagnosis				
2004-2009	1.00			
2010-2013	0.834	0.793	0.876	<0.00001
Insurance				
Private	1.00			
Medicaid	1.186	1.102	1.275	<0.00001
Medicare	1.409	1.302	1.525	<0.00001
Uninsured	1.227	1.115	1.351	<0.00001
Income				
≥$36 k	1.00			
<$36 k	1.076	1.013	1.142	0.016
Education				
<20%	1.00			
≥20%	0.908	0.858	0.96	0.0007
Distance travelled				
<30 Miles	1.00			
≥30 Miles	1.043	0.988	1.101	0.131
Diagnosis and treatment				
Same facility	1.00			
Different facility	0.866	0.823	0.911	<0.00001
Treatment delay, days				
0-11	1.00			
≥12	0.932	0.877	0.99	0.022
Treatment				
Chemotherapy only	1.00			
Chemotherapy + SCT	0.609	0.551	0.672	<0.00001

CI: Confidence intervaI; SCT: stem cell transplantation.

Table III. *Characteristics of the adolescent and young adult patient (ages 18-39 years) group.*

Factor	n	%
Gender		
Male	3459	63.95
Female	1950	36.05
Race		
White	4543	85.33
Black	523	9.82
Asian	258	4.85
Comorbidity		
0	4885	90.31
1	524	9.69
Year of diagnosis		
2004-2009	2814	57.73
2010-2013	2060	42.27
Insurance		
Uninsured	633	12.47
Private	2759	54.33
Medicaid	1453	28.61
Medicare	233	4.59
Income		
≥$36 k	1777	34.53
<$36 k	3369	65.47
Education		
<20%	2574	50.05
≥20%	2569	49.95
Distance travelled		
<30 Miles	3576	67.91
≥30 Miles	1690	32.09
Diagnosis and treatment		
Same facility	1036	9.1
Different facility	2554	47.22
Treatment delay, days		
0-11	4384	84.37
≥12	812	15.63
Treatment		
Chemotherapy only	4839	89.46
Chemotherapy + SCT	570	10.54

SCT: Stem cell transplantation.

Socioeconomic factors such as insurance, income, education, and class of care also affected outcomes in ALL. Compared to those with private insurance, patients with Medicaid, Medicare and uninsured were 18%, 40% and 22% more likely to die. Patients with lower income and education had the worst survival. Patients diagnosed and treated at different facilities were 14% less likely to die compared to those who were diagnosed and treated at the same facility. The most significant finding of our study was that SCT significantly affected outcome in ALL. Patients who underwent chemotherapy and SCT were 39% less likely to die compared to those treated with chemotherapy alone. Figure 1 shows that that the 10-year adjusted survival rate was approximately 50% for the group that received chemotherapy and SCT, as opposed to 30% for the group that did not receive SCT.

Table III presents the patient characteristics of the AYA group. Out of 5,409 patients in the AYA group, 64% were males, and 85% were White. Ninety percent had comorbidity index of zero. Regarding year of diagnosis, 42% were diagnosed between 2010 and 2013 and the rest between 2004 and 2009. More than fifty percent of the patients had private insurance and 65% had an annual income of more than

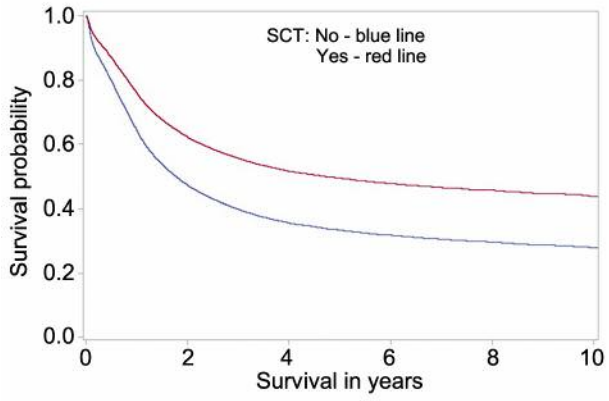

Figure 1. *Adjusted survival for patients of all age groups.*

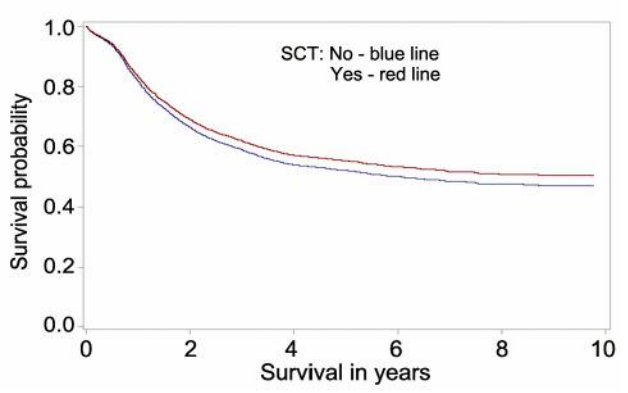

Figure 2. *Adjusted survival for patients of the adolescent and young adults (AYA) group.*

$36 k. Six-eight percent of the patient traveled less than 30 miles to their treatment center, and 52% were diagnosed and treated at the same facility. Only 10.5% of the AYA patients were treated with SCT. Table IV presents multivariate Cox regression analysis for hazard ratios of death in the AYA group. In this group, gender, race, income, distance traveled to the treatment center, facility type, class of care and delay in treatment were not associated with survival. Patients diagnosed between 2010 and 2013 were 27% less likely to die compared to the other group. Compared to privately insured patients, patients with Medicaid, Medicare and uninsured were 23%, 60% and 37% more likely to die. The most significant finding in the AYA group was that SCT did not affect survival. Figure 2 shows that the adjusted overall survival for both the groups were close to 50% at 10 years.

Discussion

Except in the AYA group of patients, our analysis of the data demonstrates a survival advantage of SCT in adult patients with ALL. Our data are consistent with previous studies. In a pediatric study on Ph+ ALL published in 2000, allogeneic SCT led to improved disease-free survival (DFS) (65 *vs.* 25%, $p<0.001$) and overall survival (OS) (72% *vs.* 42%; $p=0.002$) compared to patients who only received chemotherapy (21). Although allogeneic SCT is standard of care for Ph+ ALL, its role is less clear since the introduction of BCR–ABL targeted tyrosine kinase inhibitors. The subgroup of patients with Ph+ ALL (n=267, median age 40 years) from international collaborative E2993 trial, the 5-year OS rates with matched sibling allogeneic SCT, matched unrelated allogeneic SCT and chemotherapy alone were 44%, 36%, and 9% respectively. The incidence of transplant-related mortality was 27% in matched and 39% in unrelated donor SCT (24). For Ph+ patients National Comprehensive Cancer Network (NCCN) recommends consolidation with allo-SCT if the patient achieves complete remission (CR) and a matched sibling donor is available (4).

In a large multicenter international study (LALA 94) involving 922 patients with Ph-, aged 15-55 (mean=33) years, allogeneic SCT was associated with improved disease-free survival in high-risk Ph- ALL (25). The large multicenter MRC UKALLXII E2993 study involving 1,913 patients aged 15-59 years showed the benefit of transplant in first complete remission (CR1) in standard-risk ALL (22). The benefit of allotransplant in standard-risk ALL was also demonstrated in the HOVON study (26). A systemic review on post-remission induction therapy in adults with ALL reported significant reduction in all-cause mortality with allogeneic SCT in first CR (RR=0.88, 95% CI=0.80-0.97) (27). Our data are consistent with MRC UKALL XII/E2993, which was a large prospective randomized international collaborative study. That study demonstrated a significant increase in OS for allogeneic transplant in CR1 when compared with a standard adult ALL regimens (63% *vs.* 52%) (22). The NCCN recommends considering allo-transplant in CR1 under the following conditions for patients with ALL: Ph+ ALL, Ph- ALL with high-risk features (4).

Transplant-related mortality is a definite concern when recommending SCT for a patient. A retrospective study for over 25 years showed that transplant-related mortality has decreased from 33% to 5% and leukemic relapse remained the same (28). With the availability of haploidentical transplant, it seems that there is a donor for almost everybody (29).

Recently a significant number of studies have recommended chemotherapy only in the form on pediatric-inspired regimens for AYA with ALL (30-35). Our data show that in AYA, there is no statically significant benefit of adding transplant post-chemotherapy. Improved survival

Table IV. *Multivariate Cox regression for hazard of death by factors for the adolescent and young adult patient (ages 18-39 years) group.*

		95% CI		
Factor	HR	Lower	Upper	*p*-Value
Gender				
Male	1.00			
Female	0.983	0.892	1.083	0.72
Race				
White	1.00			
Asian	1.017	0.816	1.267	0.88
Black	1.152	0.992	1.337	0.06
Comorbidity				
0	1.00			
1	1.479	1.289	1.697	<0.00001
Year of diagnosis				
2004-2009	1.00			
20010-2013	0.735	0.664	0.814	<0.00001
Insurance				
Private	1.00			
Medicaid	1.228	1.100	1.370	0.0002
Medicare	1.596	1.296	1.965	0.00001
Uninsured	1.374	1.190	1.586	0.00001
Income				
≥$36 k	1.00			
<$36 k	1.116	0.999	1.248	0.05
Education				
<20%	1.00			
≥20%	0.804	0.721	0.896	0.00008
Distance travelled				
<30 Miles	1.00			
≥30 Miles	1.082	0.978	1.198	0.12
Diagnosis and treatment				
Same facility	1.00			
Different facility	0.943	0.854	1.040	0.24
Treatment delay, days				
0-11	1.00			
≥12	0.966	0.846	1.103	0.607
Treatment				
Chemotherapy only	1.00			
Chemotherapy + SCT	0.904	0.769	1.064	0.225

CI: Confidence intervaI; HR: hazard ratio; SCT: stem cell transplantation.

outcomes for the AYA group with ALL treated with pediatric-inspired regimens have been reported from many prospective cooperative group clinical trials performed in Europe and the United States (30-35). The NCCN recommends pediatric-inspired regimes for AYA with ALL. The largest prospective study, US intergroup C10403, on 318 AYA, demonstrated 2-year event-free survival and OS were 66% and 78% using pediatric-inspired regimens. The toxicities were manageable, with low treatment-related mortality (3%) (36, 37).

Among the other factors analyzed, age, comorbidity index, year of diagnosis, insurance, income, educations, treatment delay and class of care were all found to be significant predictors of survival in patients with ALL. Our data show that patients with lower income and education have worst outcomes. Increasing age also worsens outcomes and this is consistent with the findings of the German Multicenter Study Group for Adult ALL (GMALL) study (10). The published literature has shown 5-year survival in children to be between 80 and 90%, AYA 42-63%, 24% for those aged 40-59 years and 17% for those aged 60-69 years (10, 38, 39). Survival of AYA with ALL has improved with the adoption of pediatric-inspired regimens (15).

Ph+ ALL occurs in about 3% of pediatric ALL, compared to 25% in adults (40) The proportion of patients with Philadelphia chromosome-positive (9; 22), t (8; 14), t (14; 18), or complex aberrations increased with age (12). In the GMALL study of older patients, comorbidity score, age, and performance status before the onset of leukemia were identified as having a significant impact on early mortality (41).

A previous study on other cancer and acute myeloid leukemia showed that insurance status affects the outcomes of cancer patients (42). A study on ALL using data from SEER revealed that insurance status did not affect outcomes (43). Our data demonstrate that insurance status does affect outcome and patients with private insurance have better outcomes compared to the Medicaid, Medicare or Uninsured population. Patients who were diagnosed after 2010 had better outcomes, showing the improvement in management and therapeutic approaches for ALL.

Minimal residual disease has emerged as one of the most important prognostic factors in both pediatric and adult ALL (44-47). Unfortunately, our study has very crude data from the national database which does not have details of Ph+/– status, minimal residual disease status, molecular analysis, risk category, or type of chemotherapy for these patients. But the data suggest a benefit of transplant over the years. Stem cell transplant has led to improved survival for all age groups except the AYA group.

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