The Impact of Donor Type on Outcomes and Cost of Allogeneic Hematopoietic Cell Transplantation for Pediatric Leukemia: A Merged Center for International Blood and Marrow Transplant Research and Pediatric Health Information System Analysis

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The impact of donor type on outcomes *and* cost of allogeneic hematopoietic cell transplant for pediatric leukemia: a merged CIBMTR and PHIS analysis

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Abstract

Importance: AlloHCT may be associated with significant morbidity and mortality that result in increased healthcare utilization. To date, no multi-center comparative cost analyses have been performed specifically evaluating alloHCT in children with acute leukemia.

Objectives: To describe the relationship between survival and healthcare utilization while investigating the hypothesis that matched sibling donor (MSD) alloHCT has significantly lower inpatient healthcare utilization compared to unrelated donor (URD) and that among URD, umbilical cord blood transplants (UCB) will have higher *initial* but lower *long-term* utilization.

Design: Retrospective cohort study

Setting: Clinical and transplant outcomes data from the Center for International Blood and Marrow Transplant Research (CIBMTR) were merged with inpatient cost data from the Pediatric Health Information System (PHIS) database using a probabilistic merge methodology.

Participants: The merged dataset contained U.S. patients age 1-21 years who received alloHCT for acute leukemia from 2004-2011 with comprehensive CIBMTR data at a PHIS hospital.

Exposure: AlloHCT analyzed by donor type with specific analysis of utilization and costs using PHIS claims data.

Main Outcome: The primary outcomes of overall survival (OS), leukemia free survival (LFS), and inpatient costs were evaluated using Kaplan-Meier curves, Cox, and Poisson models.

Results: 632 patients were identified in *both* CIBMTR and PHIS. 5-year LFS was 60% for MSD, 47% for well-matched matched unrelated donor bone marrow (MUD), 48% for mismatched unrelated donor, and 45% for UCB (p=0.09). Total adjusted costs were significantly lower for MSD versus MUD by day 100 (adjusted cost ratio (ACR) 0.73, CI 0.62-0.86, p<0.001), and higher for UCB versus MUD (ACR 1.27, CI 1.11-1.45, p<0.001). By 2yrs, total adjusted costs remained significantly lower for MSD when compared to MUD (ACR 0.67, CI 0.56-0.81, p<0.001) and higher for UCB compared to MUD (ACR 1.25, 95% CI 1.02-1.52, p=0.0280).

Conclusions: UCB and MUD alloHCT provide similar survival outcomes; however, MUD alloHCT has a significant advantage in cost by day 100 and 2 years. Ongoing research is needed to determine if the cost difference among URD alloHCT remains significant with a larger sample size and/or beyond the 2 years following alloHCT.

Introduction

Allogeneic hematopoietic cell transplant (alloHCT) advances have moved the field from largely matched sibling donor (MSD) transplants to a host of other alternative donors including well-matched unrelated donor (MUD), unrelated cord blood (UCB), mismatched unrelated (MMUD), and haploidentical. Alternative donors have been utilized in pediatric acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL); yet, optimal donor selection remains somewhat unclear given their unique risks[1-4].

MSD is not always a viable option for high risk acute leukemia given the lower likelihood of having a HLA identical sibling and the urgency of treatment[5]. In these instances, alternative donor sources are considered as they are similar in terms of safety and survival[2-4]. However, these donor options may translate into marked differences in healthcare utilization (HCU).

Previous publications reported an increase in adult UCB cost compared to MSD but did not compare costs of MUD or MMUD in a multicenter analysis of pediatric acute leukemia patients [6-8]. In addition, alloHCT for childhood AML has the highest health care utilization relative to other pediatric cancers[9]. However, no studies have examined the HCU of alloHCT in the context of clinical outcomes in large, nationally representative samples nor has cost effectiveness been explored considering donor type in pediatric acute leukemia. This study performs a retrospective, multi-center comparative cost analysis of alloHCT for pediatric acute leukemia by donor type.

Methods

Data sources

Center for International Blood and Marrow Transplant Research (CIBMTR) and Pediatric Health Information System (PHIS) data have been merged using published methodology to describe *both* outcomes and HCU in alloHCT recipients[10,11]. This methodology leverages the specific and detailed outcomes data collected in CIBMTR comprehensive research forms (CRF) and HCU variables including patient-specific billing *and* clinical data from PHIS.

Merging and validating datasets

Patients transplanted for acute leukemia during the study period were identified in PHIS utilizing population-specific ICD9 diagnosis, procedure, and pharmacy codes. These patients were then identified within CIBMTR using a probabilistic algorithm[11]. We achieved 79% merge success, and institution level validation confirmed merge accuracy. The merge process occurred under the guidance of CIBMTR via the National Marrow Donor Program institutional review board.

Variables and outcomes

Outcomes analysis—Children 21 years or younger who received alloHCT for acute leukemia in the US from 2004-2011 with CRF data were included. Due to small sample size, haploidentical donor transplants (N<35) were excluded. CRFs provided clinical risk factors and outcomes including survival, graft failure, acute graft versus-host-disease (aGVHD), and chronic GVHD (cGVHD).

HCU analysis—Price-adjusted charges for each unit of service and department-specific ratio of cost-to-charge (RCC) were obtained from PHIS. Adjusted inpatient treatment costs were calculated by multiplying the adjusted charge by the relevant RCC then further adjusted to 2012 US dollars using the consumer price index. Utilization was described per inpatient day and included number of admissions, length of first and subsequent stays following alloHCT, and adjusted costs.

Costs were analyzed by total adjusted costs (TAC) and TAC per day, for 100 days and 2 years without respect to relapse. TAC was calculated for each patient as the sum of the daily costs during the entire period. TAC per day was calculated as the TAC divided by the number of inpatient days in the given period then further adjusted by 1,000 inpatient days to standardize cost comparisons and adjust for the influence of lenth of stay (LOS). Cost components including room and board, clinical (electrocardiogram, monitoring, etc.), pharmacy, lab, imaging, and supply were also analyzed.

Provider fees, donor procurement charges, indirect costs, outpatient costs, and any costs incurred at non-PHIS hospitals were not captured. Adjusted cost data only was analyzed as the primary outcome as charges and reimbursements vary across each institution and state. Patients without adjusted cost data were excluded (n=20).

Statistical Analysis

Outcomes analysis—Clinical outcomes were analyzed to provide context to HCU analysis. Patient characteristics by donor type were summarized using descriptive statistics. Kaplan-Meier curves estimated the probabilities of overall survival (OS) and leukemia-free survival (LFS). The probabilities of aGVHD, cGVHD, treatment related mortality (TRM), relapse, and engraftment were calculated using the cumulative incidence estimator to accommodate competing risks. For relapse, TRM was considered a competing risk and vice versa. Death was also a competing risk when evaluating cumulative incidence of GVHD and engraftment. Risk factors associated with engraftment, OS, LFS, TRM, relapse, GVHD were examined using the Cox proportional hazards model. Variables considered included age, sex, race, performance score, disease type and status, cytogenetics, HCT comorbidity index, duration of the first remission, recipient cytomegalovirus serostatus, donor type, donor-recipient sex match, conditioning regimen intensity, graft type, GVHD prophylaxis, antithymocyte globulin (ATG)/alemtuzumab use, and transplant period (Table 1). Models were built using backward selection and variables that met a significance level of <0.05 were held in the final model. All variables met the assumption of proportional hazards.

HCU Analysis—In univariate analyses, TAC and TAC per day were summarized using descriptive statistics and reported as median and interquartile range (IQR) by donor type, for AML and ALL separately. Differences in TAC and TAC per day by donor types were tested using Kruskal-Wallis test. Because the observed association between donor type and TAC were similar between AML and ALL in univariate analyses, the two cohorts were combined in the subsequent regression models while adjusting for disease type to gain more statistical power. In multivariate analyses, general linear regression models with gamma distribution were used due to the skewness of the costs. Adjusted cost ratios (ACR) and their 95%

confidence intervals (CI) were reported adjusting for potential confounders including disease type, age, race, insurance, disease status, CMV status, KPS, and median household income by zip code. All models used a GEE approach to account for hospital clustering. All p-values are two-sided and all analyses were done using SAS version 9.3 (Cary, NC).

Results

Demographics

632 acute leukemia patients were analyzed. Most recipients were Caucasian (75%-87%) males (54%-63%), and the majority received UCB (41%). The median age was 9 years (range <1-20) for MSD, 11 years (range <1-21) for MUD and MMUD (range 1-21), and 6 years (range <1-21) for UCB. Among those who received unrelated alloHCT, most were in CR2 (48% MUD, 61% MMUD, and 53% UCB) while most MSD (66%) were in CR1 (Table 1).

Outcomes analysis

Transplant outcomes—The 3-year OS was 66% (95%CI 57-75%) for MSD, 58% MUD (95%CI 51-65%), 56% MMUD (95%CI 45-66%) and 52% UCB (95%CI 46-58%; p=0.10). The 3-year LFS was 61% (95%CI 51-71%), 51% (95%CI 44-58%), 51% (95%CI 41-62%), and 49% (95%CI 42-55%; p=0.018), respectively (Figure 1; Table 2). The majority of deaths were attributed to the primary disease (Supplemental Data Table 2).

The 3-year TRM was lowest for MSD at 6% (95%CI 2-12%) and highest for UCB 21% (95%CI 16-26%), and MMUD 21% (95%CI 13-30%) with a statistically significant difference among donor types (p<0.001). Neutrophil engraftment by day 28 was 81% MSD (95%CI 73-88%), 92% MUD (95%CI 88-96%), 86% MMUD (95%CI 78-92%; p<0.001), and 62% UCB (95%CI 56-68%). Cumulative incidence of grade 3-4 aGVHD by day 100 was lowest for MSD 2% (95% CI 06%) and highest for UCB 20% (95% CI 15-25%) with a statistically significant difference among donor types (p<0.001). By 3 years post HCT, chronic GVHD developed in 24% MSD (95% CI 16-32%), 39% MUD (95% CI 32-46%), 44% MMUD (95%CI 34-55%), and 32% UCB (95% CI 26-38%; p=0.009), respectively (Table 2).

Multivariate analysis—Disease status at alloHCT consistently had a significant impact on survival, relapse, and TRM. While, donor type was significant in TRM, engraftment, and GVHD models (Supplemental Data Table 3).

HCU analysis

AML—The number of admissions by day 100 had a median of 1.0 (IQR 1-2) for MSD, 2.0 (IQR 1-2) MUD, 1.5 (IQR 1-2) MMUD, and 1.0 (IQR 1-2) UCB with the highest median LOS per admission of 53 days for UCB (IQR 31-80). By year 2, median admissions increased modestly to 2.0 (IQR 1-3) among MSD, 2.0 (IQR 1-5) MUD, 3.0 (IQR 2-7) MMUD, and 3.0 (IQR 1-4) UCB with an associated median LOS of 25 days (IQR 19-36), 36 days (IQR 21-64), 24 days (IQR 18-33), and 26 days (IQR 17-39), respectively.

TAC by day 100 is significantly lower for MSD (median $134,717 IQR $91,931-$176,040) compared to MUD (median $196,855 IQR $151,898-$315,949: p<0.001) and MUD compared to UCB (median $262,908 IQR $154,802-$395,207; p=0.0423) and MMUD (median $215, 824 IQR $160,596-$347,812 p=0.5577). TAC analysis demonstrated few outliers (Supplemental Figure 1). Compared to MUD, rooming, pharmacy, lab, and imaging TAC were significantly lower for MSD (p<0.000, p<0.0001, p<0.0001, p<0.000, respectively); while, rooming and lab TAC were significantly higher for UCB (p=0.0273, p<0.0001, respectively; Figure 2a). Such differences persist with respect to TAC per day which adjusts for LOS (Supplemental Figure 2a).

By 2 years, TAC of MSD (median $153,895 IQR $107,581-$287,645) remained significantly lower than MUD (median $260,796 IQR $178,863-$480,508; p<0.001); but no difference was shown between MUD and UCB (median $348,110 IQR $207,380-$582,078; p=0.1639) or MMUD (median $375,739 IQR $238,751-$553,840; p=0.0757, Figure 2a). Compared to MUD, rooming, pharmacy, lab, supply, and imaging TAC remained significantly lower for MSD (p=0.0004, p<0.0001, p=0.0026, p-0.0452, p<0.000, respectively); while, no significant difference in TAC components was found for UCB (Figure 2b). Again, similar differences persist with respect to TAC per day (Supplemental Figure 2b).

ALL—Similarly, median admissions by day 100 were 1.0 (IQR 1-3) MSD, 2.0 (IQR 1-3) MUD, 2.0 MMUD (IQR 1-2), and 1.0 (IQR 1-2) UCB with median LOS of 31 days (IQR 19-42), 27 days (IQR 20-42), 31 days (IQR 22-48), and 38 days (IQR 27-71), respectively. TAC was also significantly lower for MSD (median $145,794 IQR $114,958-$200,025) compared to MUD (median $183,721 IQR $138,923-$291,628; p=0.0055) and MUD compared to UCB (median $256,110 IQR $170,802-$363,982; p=0.0019). However, no significant difference was found between MUD and MMUD (median $185,327 IQR $136,912-$280,992; p=0.8709). Compared to MUD, room and board TAC were significantly lower for MSD (p=0.0051); while, rooming, pharmacy, *and* lab TAC were significantly higher for UCB (p=0.0084, p=0.0085, p<0.0001, respectively, Figure 2b).

The differences in TAC remained significantly lower by 2 years for MSD (median $165,001 IQR $120,815-$255,426) compared to MUD (median $243,698 IQR $158,796-$472,778; p=0.0028) MUD compared to UCB (median $319,663 IQR $207,550-$537,235: p=0.0398) and MMUD (median $260,314 IQR $139,276-$381,099; p=0.5635) despite similar changes in admissions 2.0 (IQR 1-3) MSD, 3.0 (IQR 2-7) MUD, 3.0 M (IQR 1-5) MUD, and 3.0 (IQR 1-5) UCB, and median LOS 28 (IQR 17-37), 21 (IQR 14-30), 23 (IQR 17-37), and 29 (IQR 18-52), respectively. Compared to MUD, room and board TAC remained significant; while, lab and imaging TAC also became significantly lower for MSD (p=0.0033, p=0.0235, p=0.0261, respectively). Rooming and lab TAC only remained significantly higher for UCB when compared to MUD (p=0.0328, p<0.0001, respectively, Figure 2b).

Aggregate acute leukemia multivariate analysis—In this cohort of both AML and ALL, when compared to MUD by day 100, MSD had lower TAC (ACR 0.73, 95%CI 0.62-0.87, p<0.001) and UCB had higher TAC (ACR 1.27, 95%CI 1.11-1.45, p<0.001). Compared to CMV negative patients, CMV positive patients (ACR 1.12, 95%CI 1.06-1.18,

p<0.001) had higher TAC. Similarly, compared to Caucasians, African Americans had higher TAC (ACR 1.24, 95%CI 1.09-1.42, p=0.002). When analyzing TAC per day, compared to MUD, MSD remained significant (ACR 0.88, 95%CI 0.81-0.97, p=0.008). Additionally, age > 10 years was associated with higher TAC per day (ACR 1.10, 95%CI 1.04-1.17, p<0.001) when compared to age <10 (Table 3).

By 2yrs, MSD continued to have lower TAC (ACR 0.67, 95%CI 0.56-0.81, p<0.001) and TAC per day (ACR 0.86, 95%CI 0.79-0.94, p=0.001); and TAC of UCB remained significantly higher than MUD (ACR 1.25, 95%CI 1.02-1.52, p=0.028). African Americans had higher TAC by 2 years compared to Caucasians (ACR 1.20, 95%CI 1.04-1.38, p=0.009). Children > 10 years had higher TAC and TAC per day as compared to age <10 (ACR 1.21, 95%CI 1.09-1.36, p<0.0001and ACR 1.13, 95%CI 1.07-1.20, p<0.001, respectively) (Table 3).

To further evaluate the potential impact of mortality, we repeated the analyses restricting to survivors only and the results remain similar (Supplemental Table 5).

Discussion

This study provides new insight into unrelated donor outcomes *and* cost of alloHCT for acute leukemia by utilizing a multicenter sample. Analysis showed expected differences by donor type in neutrophil engraftment, GVHD, TRM, and LFS. However, these differences did not directly correlate to differences in cost.

MSD performed better in traditional outcomes and cost. Previous studies also showed decreased MSD cost when compared to other donor sources; however, these differences were associated with performance status, graft failure, and transplant related end-organ damage within the first 100 days[12]. These findings suggest that over the long-term the lower TRM associated with MSD provides both survival and cost advantages.

Among unrelated alloHCT, increased GVHD risk was hypothesized as the etiology of poorer outcomes and increased HCU[13,14]. However, when compared to MUD, UCB was associated with *higher* aGVHD and higher costs. This is in contrast to published reports showing rates of GVHD in UCB as substantially lower than that of MUD[5]. Our cohort was comparable in terms of types of conditioning but had more African American recipients and mismatched products. This suggests another possible etiology of increased GVHD and/or costs that could not be analyzed in this study[15]. Specifically, the primary exposure of interest in this study is donor type; efforts to separate GVHD in the analysis may attenuate that main exposure. This finding does not provide sufficient evidence to change the current center-specific trend prioritizing MUD over UCB and quantifies the combined financial impact of delayed neutrophil engraftment, prolonged inpatient LOS, and GVHD. Therefore, efforts to enhance engraftment including cord blood expansion may mitigate the early cost impact but may not alter the GVHD related cost. The latter may also be confounded by delayed immune reconstitution, prolonged immunosuppression, or infection[16]. Future studies investigating causative factors for increased cost over time as well as the impact of intensive care, role of

haploidentical transplant, and use of newer UCB technologies are needed to better analyze unrelated donor costs.

African Americans were also shown to have higher costs. Previous publications have shown poorer clinical outcomes among African Americans likely due to delayed diagnosis, poverty, and reduced access to healthcare resources[17-21]. In our cohort, most African Americans received UCB transplants. However, cost analysis of race against donor type did not reveal any potential causative factors like disease status, insurance type, and household income. In addition, African Americans did not have a significant difference in LFS, OS, or TRM; therefore, the increase in cost may be attributed to other factors not analyzed in this study including donor age, pharmacogenomics, and infectious complications that must be further explored [15,16,22,23]. This evidence *does* support a preference toward MUD for African Americans; however, this study *cannot* definitively prioritize one donor source over another as insufficient numbers of haploidentical transplants were available for analysis. These findings highlight the importance of a more comprehensive analysis in a larger cohort that incorporates *all* available donor types throughout a longer time period to better establish the differences in cost.

Limitations

As a retrospective study, predefined variables and data are inherently limited. Furthermore, the CRF data represented a sample of patients identified by CIBMTR. This is somewhat mitigated by the addition of PHIS to increase data quality and availability. Despite this enrichment of data, a lower than expected merge yield was found; yet, outcomes analysis was similar to published reports suggesting that cost analysis should also be representative[24,25].

PHIS represents over 80% of pediatric free-standing hospitals and therefore is considered a representative sample. Yet, insufficient outpatient HCU data was available for analysis and procurement fees were unavailable within PHIS. Previous publications have shown that unrelated alloHCT costs remained similar when graft acquisition costs or outpatient costs were considered[10,12]. Therefore, PHIS was selected due to its ability to capture both patient-specific encounter level data as well as cost instead of other more comprehensive claims databases with the assumption that the absence of outpatient and procurement costs would be negligible. Compared to existing data, the absence of outpatient cost may have a substantial impact on long term alloHCT cost in particular for ALL treatment which occurs primarily in the outpatient setting. However, published analysis has indicated that a substantial difference in outpatient cost would be needed to influence the significance of inpatient costs[24].

Another potential limitation is the impact of center level variability. Specifically, donor selection may vary by center; our statistical analysis adjusted for clustering and potential center level effects. However, we were unable to account for other center related issues specifically distance from transplant center. Although this data has not shown a clear impact on outcomes, it could certainly impact the frequency with which patients utilized transplant center resources and any care that occurred at non-PHIS centers but was not captured[26,27].

In addition, this study includes a heterogeneous population by disease, donor type, graft source, and conditioning regimen. Survival outcomes of this cohort are similar to published estimates suggesting that our cohort heterogeneity had limited influence on the outcomes analysis[24, 25]. In addition, multivariate analysis of both outcomes and cost were performed to elucidate any confounders.

Finally, this study excluded data on haploidentical transplant; promising clinical outcomes to date suggest this is as another viable means of expanding the donor pool for patients with acute leukemia[1,28,29]. Ultimately, as the field advances with changes in conditioning regimens, other modified donor source options, and the broad availability of CAR-T therapy, ongoing cost effectiveness analysis will be needed.

Conclusion

This study builds on a research methodology paradigm that allows for analysis of both clinical and financial outcomes in the absence of a singular, exhaustive data source [10,11,24,25,30]. These results support the use of MSD, when available, and enhances our understanding of risk factors associated with poor outcomes and increased costs following unrelated alloHCT. Improvement in unrelated alloHCT clinical outcomes for pediatric acute leukemia have the potential to have the highest clinical and financial impact. These results provide a stepping stone for future research and guidance into the key variables that may impact clinical outcomes and cost among newer, novel curative therapies for children with acute leukemia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Matched sibling donor transplant has a survival and cost advantage over unrelated donor transplants
- Matched unrelated donor and unrelated cord blood have similar survival outcomes
- Among unrelated donor transplants, matched unrelated donor transplant has a cost advantage

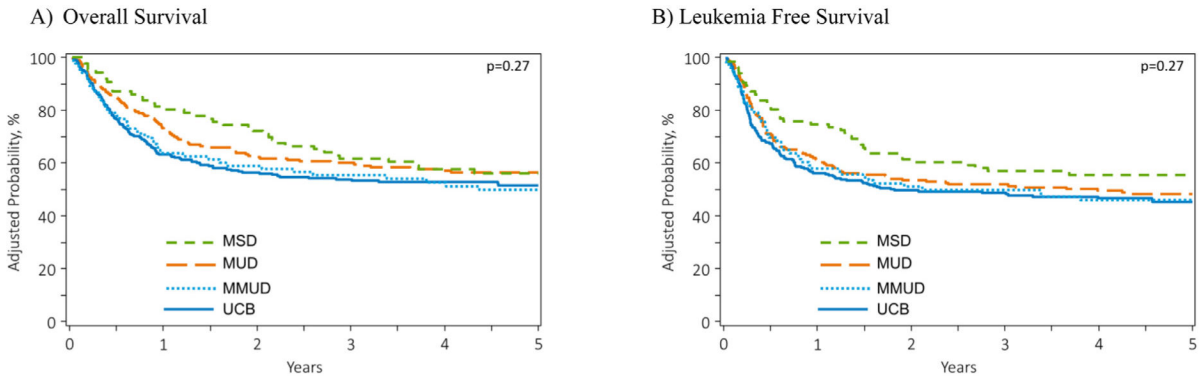

Figure 1:

Multivariate Analysis of Survival by Donor Type

Abbreviations: MSD - matched sibling donor, MUD - matched unrelated donor, MMUD - mismatched unrelated donor, UCB - unrelated umbilical cord blood transplants

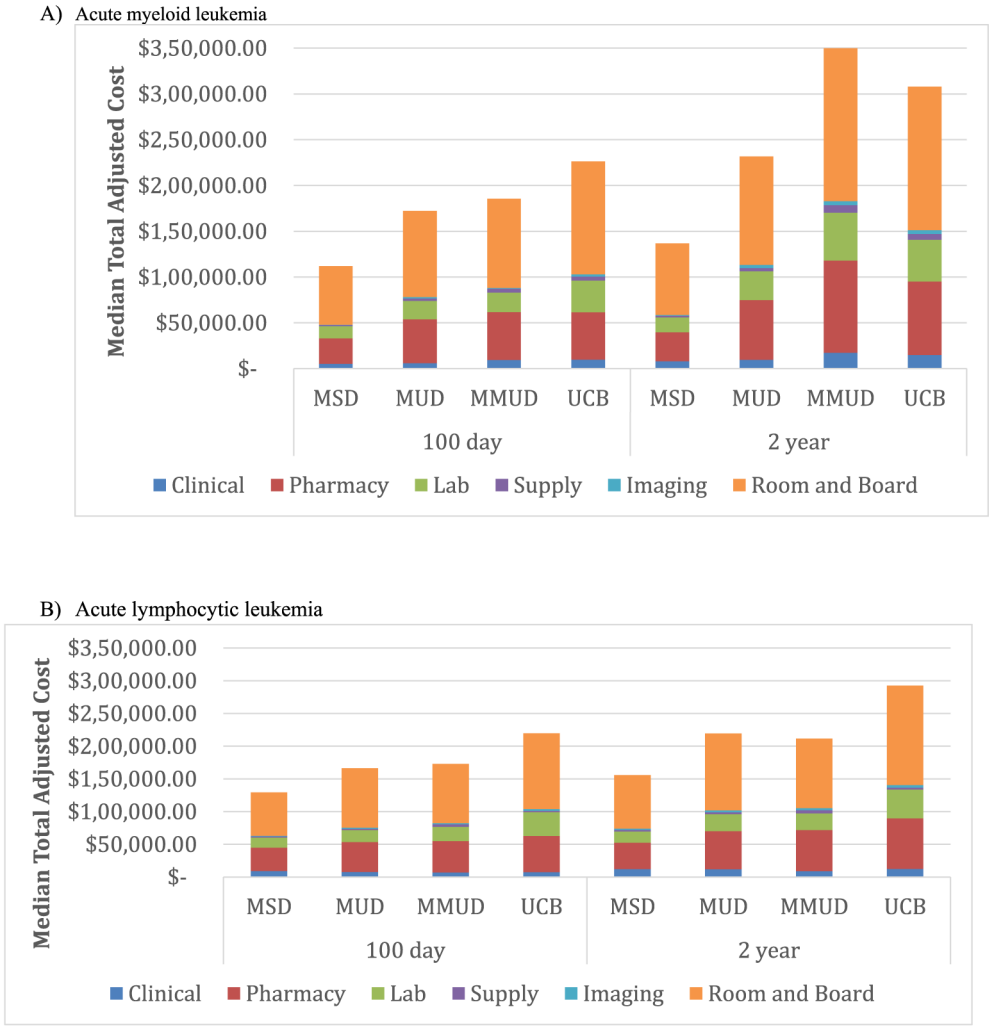

Figure 2.

Categories of median total adjusted cost by donor type

Abbreviations: MSD - matched sibling donor, MUD - matched unrelated donor, UCB - unrelated umbilical cord blood transplants, MMUD - mismatched unrelated donor

Table 1.

Characteristics of US patient ≤21 years of age who underwent an allogeneic HCT for **AML and ALL** between 2004-2011, **reported to** the CIBMTR

	MSD	MUD	MMUD	UCB	p-value
Number of patients	102 (16)	186 (29)	87 (14)	257 (41)	
Number of centers	24	31	29	34	
Patient related					
Age at transplant, years					< 0.001[a]
Median (range)	9 (<1-20)	11 (<1-21)	11 (1-21)	6 (<1-21)	<0.001[b]
<1	5 (5)	3 (2)	0	8 (3)	
1-9	51 (50)	82 (44)	34 (39)	181 (70)	
10-21	46 (45)	101 (54)	53 (61)	68 (26)	
Weight, median (range), kg	34 (6-121)	38 (7-178)	41 (8-157)	22 (7-181)	< 0.001[b]
Gender					0.26[a]
Male	59 (58)	117 (63)	54 (62)	139 (54)	
Female	43 (42)	69 (37)	33 (38)	118 (46)	
Race					< 0.001[a]
Caucasian	76 (75)	161 (87)	68 (78)	196 (76)	
African-American	5 (5)	7 (4)	8 (9)	29 (11)	
Other *	18 (17)	3 (1)	5 (6)	18 (8)	
Missing	3 (3)	15 (8)	6 (7)	14 (5)	
Karnofsky score prior to transplant					0.08[a]
<90	10 (10)	18 (10)	9 (10)	31 (12)	
>=90	92 (90)	154 (83)	73 (84)	218 (85)	
Missing	0	14 (8)	5 (6)	8 (3)	
Disease related					
Disease					0.008[a]
AML de novo	52 (51)	83 (45)	22 (25)	102 (40)	
Secondary AML	8 (8)	14 (8)	6 (7)	13 (5)	
ALL	42 (41)	89 (48)	59 (68)	142 (55)	
Disease status					< 0.001[a]
Early (CR1)	67 (66)	67 (36)	26 (30)	87 (34)	
Intermediate (CR2+)	30 (29)	90 (48)	53 (61)	136 (53)	
Advanced (PIF,Rel)	3 (3)	29 (16)	8 (9)	33 (13)	
Missing	2 (2)	0	0	1 (<1)	
HCT-CI - no. (%)					< 0.001[a]
0	127 (49.4)	40 (39.2)	44 (23.7)	12 (13.8)	
1	11 (4.3)	0	4 (2.2)	1 (1.1)	
>=2	8 (3.1)	3 (2.9)	7 (3.8)	0	

	MSD	MUD	MMUD	UCB	p-value
Year of TX <=2007	111 (43.2)	59 (57.8)	131 (70.4)	74 (85.1)	
Cytogenetics scoring					0.005[a]
AML[1]					
Favorable	2 (2)	8 (4)	7 (8)	14 (5)	
Intermediate	56 (55)	74 (40)	16 (18)	83 (32)	
Poor	2 (2)	12 (6)	2 (2)	10 (4)	
Not tested/Missing	0	3(1)	3 (3)	8 (3)	
ALL[2]					0.05[a]
Normal	15 (15)	26 (14)	13 (15)	40 (16)	
Poor	9 (9)	24 (13)	12 (14)	44 (17)	
Other	17 (17)	32 (17)	21 (24)	47 (18)	
Not tested/Missing	1 (<1)	7 (4)	13 (15)	11 (5)	
Transplant related					
Months to transplant for CR1 (range)	3 (<1-9)	3 (<1-35)	3 (<1-12)	3 (<1-18)	0.62[b]
Months of CR1 for CR2 (range)	23 (2-60)	17 (<0.3-151)	27 (2-114)	14 (<0.2-101)	0.004[b]
Recipient CMV					
–	43 (42)	95 (51)	40 (46)	136 (53)	0.41[a]
+	57 (56)	90 (48)	46 (53)	120 (47)	
Missing	2 (2)	1 (<1)	1 (1)	1 (<1)	
Conditioning intensity**					< 0.001[a]
MAC-TBI	53 (52)	143 (77)	75 (86)	187 (73)	
MAC-Chemo	49 (48)	43 (23)	12 (14)	70 (27)	
GVHD Prophylaxis					<0.001[a]
Ex-vivo T cell depletion/ CD34 selection	1 (0.4)	4 (3.9)	15 (8.1)	18 (20.7)	
FK506 based	58 (22.6)	21 (20.6)	73 (39.2)	31 (35.6)	
CSA based	193 (75.1)	71 (69.6)	97 (52.2)	36 (41.4)	
Other***/ Missing	5 (1.9)	6 (5.9)	1 (0.5)	2 (2.3)	
ATG/Alemtuzumab					<0.001[a]
ATG alone	0	58 (31)	19 (22)	159 (62)	
Alemtuzumab alone	2 (2)	36 (19)	27 (31)	3 (1)	
No ATG or Alemtuzumab	100 (98)	92 (49)	41 (47)	95 (37)	
Year of transplant					<0.001[a]
2004-2007	59 (58)	131 (71)	74 (85)	111 (43)	
2008-2011	43 (42)	55 (29)	13 (15)	146 (57)	
Median follow-up of survivors (range), months	67 (4-124)	70 (22-124)	73 (10-120)	60 (3-121)	

Abbreviations:

AML=acute myeloid leukemia, ALL=acute lymphocytic leukemia, MSD=matched/HLA identical sibling donor bone marrow, MUD=well-matched unrelated donor bone marrow (8/8/, 10/10), MMUD=mismatched unrelated donor marrow, UCB=single umbilical cord blood, CR=complete

response/remission, HCT-CI=hematopoietic cell transplantation comorbidity index, CMV=cytomegalovirus, HLA=human leukocyte antigen, MAC=myeloablative conditioning, TBI=total body irradiation, Bu=busulfan, Cy=cyclophosphamide, Flu=fludarabine, Mel=melphalan, CSA=cyclosporine, FK506=tacrolimus, ATG=antithymocyte globulin

Footnotes

Hypothesis testing: a: Pearson chi-square test b: Kruskal-Wallis test.

*Asian/Pacific Islander, Native American, Other (see supplemental table 1 for detail)

**conditioning intensity subtypes listed in supplemental table 1

***UCB: mtx+siro(n=1); MSD: mtx(n=3); cor+mtx(n=2); cor + mtx + urso(n=1);MMUD: cor+mab+mtx(n=1).

1: cytogenetic scoring: “poor” risk cytogenetics: −7, −5, del (5q); “favorable” cytogenetics: t(8;21), t(15; 17) and inv(16); “intermediate”: all others.

2: cytogenetic scoring: “poor” risk cytogenetics: t(9;22), t(4;11), t(8;14), t(14; 18), hypodiploid (<46), complex (≥ 3 abnormalities).

Table 2.

Univariate analysis of outcomes

	MSD		MUD		MMUD		UCB		
Outcomes	**N**	**Prob (95% CI)**	**N**	**Prob (95% CI)**	**N**	**Prob (95% CI)**	**N**	**Prob (95% CI)**	**p-value**
Neutrophil engraftment	102		186		87		255		**<0.001**
28-day		81 (73-88)%		92 (88-96)%		86 (78-92)%		62 (56-68)%	
Platelet recovery	101		184		85		247		**<0.001**
28-day		46 (36-55)%		49 (42-57)%		41 (31-52)%		9 (6-13)%	<0.001
100-day		97 (92-99)%		88 (83-92)%		84 (76-91)%		74 (68-79)%	<0.001
Grade 2-4 acute GVHD	102		186		87		257		**<0.001**
100-day		4 (1-9)%		34 (28-41)%		37 (27-47)%		41 (35-47)%	<0.001
Grade 3-4 acute GVHD	102		186		87		257		**<0.001**
100-day		2 (0-6)%		8 (4-12)%		10 (5-18)%		20 (15-25)%	<0.001
Chronic GVHD	101		182		85		253		**0.02**
1-year		22 (15-31)%		37 (30-44)%		36 (26-47)%		30 (24-36)%	0.04
3-year		24 (16-32)%		39 (32-46)%		44 (34-55)%		32 (26-38)%	0.009
Cumulative incidence of CMV reactivation	102		131		63		208		0.16
6 months		7 (3-13)%		11 (7-17)%		19 (10-30)%		14 (10-19)%	0.08
1-year		8 (3-14)%		12 (7-18)%		19 (10-30)%		15 (11-21)%	0.11
Treatment related mortality	101		184		87		254		**0.003**
1-year		4 (1-9)%		11 (7-16)%		18 (11-27)%		19 (14-24)%	<0.001
3-year		6 (2-12)%		15 (10-21)%		21 (13-30)%		21 (16-26)%	<0.001
Leukemia free survival	101		184		87		254		**0.04**
1-year		78 (69-86)%		60 (53-67)%		60 (49-70)%		56 (50-62)%	<0.001
3-year		61 (51-71)%		51 (44-58)%		51 (41-62)%		49 (42-55)%	0.18
Relapse	101		184		87		254		0.55
1-year		18 (11-26)%		29 (23-36)%		22 (14-31)%		25 (20-31)%	0.18
3-year		33 (24-42)%		34 (27-41)%		28 (19-38)%		31 (25-36)%	0.76
Overall survival	102		186		87		257		**0.05**
1-year		83 (75-90)%		72 (65-78)%		64 (54-74)%		62 (56-68)%	<0.001
3-year		66 (57-75)%		58 (51-65)%		56 (45-66)%		52 (46-58)%	0.10

Table 3.

Multivariate health care utilization analysis

TIME INTERVAL			100 DAY				2 YEAR			
COST VARIABLE			TAC		TAC PER DAY		TAC		TAC PER DAY	
PARAMETER	**CATEGORY**	**N**	**ACR(95% CI)**	**P-VALUE**	**ACR(95% CI)**	**P-VALUE**	**ACR(95% CI)**	**P-VALUE**	**ACR(95% CI)**	**P-VALUE**
Donor type				**0.0092**		0.1718		**0.0246**		0.0895
	MSD	102	0.73 (0.62-0.87)	**0.0003**	0.88 (0.81-0.97)	**0.0076**	0.67 (0.56-0.81)	**<0.0001**	0.86 (0.79-0.94)	**0.0012**
	MUD	186	1.00	-	1.00	-	1.00	-	1.00	-
	MMUD	87	1.05 (0.81-1.36)	0.7076	1.00 (0.89-1.11)	0.9665	1.11 (0.81-1.53)	0.5132	0.99 (0.92-1.07)	0.8460
	UCB	257	1.27 (1.11-1.45)	**0.0003**	1.04 (0.94-1.14)	0.4699	1.25 (1.02-1.52)	**0.0280**	1.06 (0.96-1.17)	0.2885
Age at transplant				0.1686		**0.0323**		**0.0251**		**0.0120**
	1-9 years	348	1.00	-	1.00	-	1.00	-	1.00	-
	≥10 years	268	1.10 (1.00-1.20)	**0.0407**	1.10 (1.04-1.17)	**0.0006**	1.21 (1.09-1.36)	**0.0005**	1.13 (1.07-1.20)	**<0.0001**
	<1year	16	0.92 (0.70-1.21)	0.5416	0.96 (0.82-1.12)	0.6114	0.97 (0.68-1.37)	0.8437	0.99 (0.86-1.13)	0.8431
Race				0.1721		0.2590		0.2263		0.3712
	Caucasian	501	1.00	-	1.00	-	1.00	-	1.00	-
	African	49	1.24 (1.09-1.42)	**0.0016**	1.10 (0.99-1.21)	0.0524	1.20 (1.05-1.38)	**0.0089**	1.10 (0.99-1.22)	0.0850
	Other	44	1.13 (0.92-1.39)	0.2325	1.04 (0.96-1.13)	0.3519	0.97 (0.76-1.23)	0.7917	1.05 (0.95-1.16)	0.3780
	Missing	38	0.94 (0.82-1.08)	0.3599	0.95 (0.90-1.01)	0.0816	1.00 (0.75-1.34)	0.9909	0.96 (0.90-1.04)	0.3369
Recipient CMV				<0.0001		0.2998		0.1271		0.1725
	Negative	314	1.00	-	1.00	-	1.00	-	1.00	-
	Positive	313	1.12 (1.06-1.18)	**<0.0001**	1.03 (0.98-1.08)	0.2998	1.11 (0.97-1.27)	0.1271	1.04 (0.98-1.09)	0.1725
Income				0.5403		0.3145		0.6153		0.1793
	1st quartile	152	1.00	-	1.00	-	1.00	-	1.00	-
	2nd quartile	151	1.00 (0.89-1.13)	0.9458	0.95 (0.90-1.01)	0.1059	1.03 (0.88-1.20)	0.7130	0.94 (0.89-0.99)	**0.0331**
	3rd quartile	157	1.01 (0.87-1.17)	0.9247	1.01 (0.93-1.09)	0.8953	1.16 (0.95-1.43)	0.1459	0.99 (0.91-1.08)	0.8746
	4th quartile	160	0.91 (0.81-1.02)	0.1116	0.96 (0.90-1.03)	0.2357	0.99 (0.83-1.18)	0.9427	0.95 (0.89-1.03)	0.1983
Disease status				0.1763		0.4844		0.8851		0.2342
	Early	247	1.00	-	1.00	-	1.00	-	1.00	-
	Intermediate (<1yr)	80	1.05 (0.92-1.21)	0.4487	1.05 (0.96-1.15)	0.3120	0.95 (0.77-1.19)	0.6660	1.05 (0.96-1.14)	0.2871

TIME INTERVAL			100 DAY				2 YEAR			
COST VARIABLE			TAC		TAC PER DAY		TAC		TAC PER DAY	
PARAMETER	CATEGORY	N	ACR(95% CI)	P-VALUE	ACR(95% CI)	P-VALUE	ACR(95% CI)	P-VALUE	ACR(95% CI)	P-VALUE
	Intermediate (>1yr)	181	0.97 (0.84-1.11)	0.6444	1.00 (0.93-1.08)	0.9474	0.91 (0.75-1.12)	0.3957	1.01 (0.94-1.08)	0.7929
	Intermediate Missing	48	1.06 (0.82-1.36)	0.6766	1.04 (0.92-1.18)	0.5083	1.01 (0.76-1.35)	0.9212	1.06 (0.95-1.17)	0.3026
	Advanced	73	0.85 (0.72-1.01)	0.0655	0.96 (0.88-1.04)	0.3052	0.88 (0.69-1.12)	0.2958	0.94 (0.87-1.02)	0.1161

TAC=total adjusted cost, adjusted based 2012 dollars, and in multivariate modeling, a priori confounders and hospital clustering; TAC per day=TAC per actual hospital days adjusted by a standard 1000 inpatient days; ACR=adjusted cost ratio