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Comparison of Graft Acquisition and Early Direct Charges of Haploidentical Related Donor Transplantation versus Umbilical Cord Blood Transplantation

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A B S T R A C T
Alternative donor allogeneic hematopoietic cell transplants (HCTs), such as double umbilical cord blood transplants (dUCBT) and haploidentical related donor transplants (haplo-HCT), have been shown to be safe and effective in adult patients who do not have an HLA-identical sibling or unrelated donor available. Most transplant centers have committed to 1 of the 2 alternative donor sources, even with a lack of published randomized data directly comparing outcomes and comparative data on the cost-effectiveness of dUCBT versus haplo-HCT. We conducted a retrospective study to evaluate and compare the early costs and charges of haplo-HCT and dUCBT in the first 100 days at 2 US transplant centers. Forty-nine recipients of haplo-HCT (at 1 center) and 37 with dUCBT (at another center) were included in the analysis. We compared graft acquisition, inpatient/outpatient, and total charges in the first 100 days. The results of the analysis showed a significantly lower cost of graft acquisition and lower total charges (for 100-day HCT survivors) in favor of haplo-HCT. Importantly, to control for the obvious shortcomings of comparing costs at 2 different transplant centers, adjustments were made based on the current (2018) local wage index and inflation rate. In the absence of further guidance from a prospective study, the cost analysis in this study suggests that haplo-HCT may result in early cost savings over dUCBT and may be preferred by transplant centers and for patients with more limited resources.

INTRODUCTION

Allogeneic hematopoietic cell transplantation (allo-HCT) is a curative treatment option for advanced or high-risk hematologic malignancies [1]. With shrinking family size and a limited donor pool for ethnic minorities, the availability of an HLA-matched sibling or unrelated donors can be a challenge [2]. In addition, because an unrelated donor search can take up to 4 months [3], many high-risk patients can relapse or succumb to their disease while awaiting identification of a suitably matched donor [4]. Umbilical cord blood (UCB) and haploidentical (haplo) related donor grafts are generally readily available for most patients lacking a matched related or unrelated donor [5-9]. The early challenge of transplant complications related to delayed engraftment in UCB transplant (UCBT) can be overcome with the use of 2 cord blood units (CBUs) or by various CBU expansion platforms [10,11]. In contrast, overcoming the MHC barrier and preventing graft-versus-host disease (GVHD) in haplo related donor transplantation (haplo-HCT) has been made possible through the adoption of a post-transplantation cyclophosphamide (PT-CY) platform [12-14]. Although double UCBT (dUCBT) and haplo-HCT have been shown to be safe and effective [6,15], there are no published randomized studies directly comparing outcomes between the 2 donor sources [16].

Two parallel (nonrandomized) phase II trials were conducted using similar reduced-intensity conditioning (RIC) regimens and either haplo-bone marrow transplant (Blood and Marrow Transplant Clinical Trials Network [BMT CTN] 0603) or dUCB units (BMT CTN 0604) to assess the efficacy and safety of these 2 alternative donor transplants [6]. The outcomes appeared comparable in terms of survival, neutrophil recovery, and incidence of GVHD, even though no direct comparison of outcomes was conducted between the 2 donor sources. The results of these trials led to the recently completed phase III randomized study of dUCBT versus haplo-HCT (BMT CTN 1101, NCT 01597778) using RIC.

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Allo-HCT is associated with significant costs and financial burden on patients and healthcare resources [17,18]. With regards to the direct donor-associated costs, the acquisition cost of the dUCB graft is potentially higher than haplo grafts [9,18,19]. In addition, there may be differences in count recovery kinetics, infectious complications, and incidence/severity of GVHD between the 2 sources that may drive early post-transplant costs. This is illustrated by the results of a retrospective French study that evaluated cost-effectiveness of single UCBT versus dUCBT using a Markov decision analysis model showing that dUCBT was more cost-effective and had better quality-adjusted life-years within 4 years of follow-up [20]. Although cost-effectiveness analysis is conducted parallel to the BMT CTN 1101 to prospectively address the economic value of alternative donor (haplo-HCT versus dUCBT) sources, no other published studies compare early direct cost after the 2 transplant approaches [21]. To address this question we compared the early (100 days after HCT) and direct costs between dUCBT and haplo-HCT including graft acquisition costs and inpatient and outpatient charges in a retrospective fashion using data on consecutive patients undergoing haplo-HCT at the Medical College of Wisconsin, Milwaukee and dUCBT at West Virginia University, Morgantown. Our hypothesis was that the total direct medical care costs will be significantly greater for patients receiving dUCB compared with haplo-HCT recipients.

METHODS

Patients

All consecutive adult patients undergoing a PT-CY–based T cell–replete haplo-HCT at the Medical College of Wisconsin and dUCBT at West Virginia University during March 2009 to March 2017 were included in this retrospective analysis. Institutional Review Board approval was obtained at both centers. Intensity of conditioning regimens was classified as myeloablative conditioning versus RIC/nonmyeloablative conditioning based on consensus criteria [22]. Granulocyte colony-stimulating factor–mobilized peripheral blood or nonstimulated bone marrow haplo grafts and dUCB grafts were infused on day 0. All haplo-HCT patients received uniform GVHD prophylaxis with PT-CY, tacrolimus, and mycophenolate mofetil as described previously [23-25]. UCBT patients received tacrolimus and mycophenolate mofetil, with antithymocyte globulin (ATG) given per physician discretion for prevention of GVHD. Anti-infective prophylaxis was administered according to institutional guidelines. Granulocyte colony-stimulating factor was started at a dose of 5 μg/kg s.c. on day +5 for haplo-HCT and dUCBT and was continued until neutrophil recovery.

All patients were followed within the respective transplant centers from the time of pre-HCT evaluation until at least 100 days post-HCT. In both centers all hospitalizations within the first 100 days of HCT are exclusively in a dedicated inpatient unit, and all outpatient visits within the first 100 days occur in the transplant clinic/day hospital. Hence, the institutional accounting departments at both centers capture all relevant medical costs for the first 100 days except costs for outpatient prescription drugs, including drugs administered through home care services.

Definitions and Study Endpoints

For the early post-HCT cost evaluation and comparison, we collected the direct medical care costs charged to insurance payers at the 2 transplant centers (not the actual insurance reimbursements to the institution). Analysis of cost comparison was based on graft acquisition costs and direct medical care charges up to day +100 post-HCT (inclusive of nursing, laboratory, imaging, procedural and facility charges, cost of blood products, cost of medications provided by the inhouse pharmacy during hospitalization, or infusion visits) beginning with first the day of the index hospitalization for HCT. Graft acquisition cost of haplo-HCT consisted of costs for donor evaluation including HLA typing, apheresis procedure or bone marrow harvest (depending on the product used), and graft processing and storage, whereas for dUCBT recipients cost of graft acquisition included those for searching the cord blood bank inventory, confirmatory HLA typing of CBUs, cost of the UCB units, and shipping of CBUs to the transplant center. Prescription drug costs were not included in the analysis [26]. The extracted costs were inflation-adjusted to 2018 dollars using the Medical Care Consumer Price Index [27]. Adjustment for variation in charges between the 2 transplant centers was conducted based on fiscal year 2018 hospital-specific wage index used by Centers for Medicaid & Medicare Services (CMS), converting values to represent national average [28]. Disease risk index (DRI) and HCT-specific comorbidity index (HCT-CI) were calculated based on established definitions [29,30].

Neutrophil engraftment was defined as achieving an absolute neutrophil count ≥ 500/μL for 3 consecutive days. Platelet recovery was defined as achieving a platelet count ≥ 20,000/μL unsupported by platelet transfusions for 7 days. Primary graft failure was defined as failure to achieve an absolute neutrophil count ≥ 500/μL and/or donor chimerism ≥ 5% (unsorted blood or marrow or peripheral blood T cell) at any point post HCT [31]. Acute GVHD was defined and graded according to previously described criteria [15]. Overall survival (OS) was defined as the time from transplantation until death, and surviving patients were censored at last follow-up. Progression-free survival (PFS) was defined as time from transplantation to either disease relapse/progression or death from any cause. Patients alive and progression-free were censored at the last follow-up. Nonrelapse mortality (NRM) was defined as death without prior evidence of disease relapse/progression with relapse as a competing event. NRM was considered a competing event for calculating cumulative incidence of relapse/progression. For GVHD, death without the event was considered a competing event.

Statistical Analysis

Patient demographics and clinical characteristics were summarized using frequencies with percentages for categorical variables and median with range for continuous outcomes and compared between the 2 groups using the chi-square test and Wilcoxon rank-sum test, respectively. Comparison of patient, disease, and transplant characteristics was performed using chi-square, Fisher's exact, or Wilcoxon's rank sum test as appropriate. Survival distributions were estimated using the Kaplan-Meier method and compared between groups using the log-rank test. The Nelson-Aalen estimator was used to estimate cumulative incidence of acute GVHD, with Gray's test for group comparisons.

The primary endpoint of this study was to compare direct medical charges among recipients of haplo-HCT and dUCBT. Wilcoxon's rank-sum test was used for the primary analysis because of the skewness of the distribution of costs. We also wanted to explore factors associated with increased costs of transplantation. To simplify the comparison between the 2 types of transplants, charges are also presented as charge per-day survived (in dollars). Covariate adjusted analysis of charges was conducted: Charges were modeled via linear regression on a logarithmic scale to improve normality of the residuals. The model coefficients were exponentiated for reporting and can be interpreted as the multiplicative effect of the predictors on the median charge. In addition to donor graft type, age at HCT, Karnofsky Performance Score, HCT-CI, prior autologous HCT, and DRI were included as baseline covariates. ATG use and $CD34^+$ cell dose were very highly correlated with donor type and were therefore not examined as covariates in the model. HLA match status was fully confounded with transplant type and therefore was not included as a separate variable.

To ensure that any differences were not due to varying life expectancy, the number of days alive of the first 100 post-transplant were included as an adjustment covariate. Based on exploratory analysis showing a nonlinear effect of days alive, the effect of this covariate was modeled by a cubic spline [32]. The interaction of donor type with all baseline predictors was evaluated, but only the significant interactions are presented in the final model. No other model selection was performed. All *P* values reported are 2-sided. Analyses were performed using SAS, version 9.4 (SAS Institute, Cary, NC).

RESULTS

Patient and Transplant Characteristics

Included in the study were consecutive patients undergoing dUCBT (n = 37) and haplo-HCT (n = 49) at West Virginia University and the Medical College of Wisconsin, respectively. As expected, differences were noted in baseline characteristics between patients in the 2 groups (Table 1). Compared with the dUCBT group, patients in the haplo-HCT group were older (median age 44 versus 55, *P* = .02) and had a higher proportion of patients with intermediate- or high-risk DRI (62% versus 92%, *P* = .002) and HCT-CI score ≥ 3 (27% versus 57%, *P* = .005). Conditioning regimen was predominantly fludarabine- and cyclophosphamide-based (approximately 80%) at both centers. However, a significant proportion of patients undergoing dUCBT received ATG as part of their conditioning (78%) versus none of the haploHCT patients. All dUCBT patients received total body irradiation compared with 81% of the haplo-HCT group (*P* = .01). All patients undergoing haplo-HCT and none of the dUCBT patients received PT-CY. The median $CD34^+$ cell dose infused for dUCBT and haplo-HCT was $.1 \times 10^6$/kg body

Table 1
Patient and Transplantation Characteristics

	dUCBT(n = 37)	Haplo-HCT (n = 49)	P
Median age at HCT, yr (range)	44 (21-63)	55 (20-74)	.02
Male sex	19 (51)	28 (57)	.59
Diagnosis			.25
MDS/AML	18 (49)	25 (51)	
ALL	4 (11)	6 (12)	
Lymphoma	10 (27)	8 (16)	
CML	1 (3)	1 (2)	
CLL	2 (5)	0 (0)	
Other	2 (5)	9 (18)	
CIBMTR DRI			.002
Low	12 (32)	2 (4)	
Intermediate	15 (40)	33 (67)	
High	8 (22)	12 (24)	
Not applicable	2 (5)	2 (4)	
Remission status at HCT			.64
Complete/partial remission	30 (81)	36 (73)	
Stable disease	2 (5)	6 (12)	
Refractory disease	5 (13)	7 (14)	
Median HCT-CI score (range)	1 (0-8)	3 (0-8)	.01
Categorized HCT-CI			.005
≥3	10 (27)	28 (57)	
<3	27 (73)	21 (43)	
Median KPS (range)	80 (70-100)	80 (50-100)	.44
KPS < 90	23 (62)	25 (51)	.30
Prior auto-HCT	6 (16)	10 (20)	.62
Conditioning Intensity			.19
MAC	8 (22)	17 (35)	
RIC/NMA	29 (78)	32 (65)	
Graft source			
Bone marrow	0 (0)	22 (45)	
Peripheral blood	0 (0)	27 (55)	
UCB	37 (100)	0 (0)	
ATG used in conditioning	29 (78)	0 (0)	NA
PT-CY/MMF/CNI	0	49 (100)	NA
CNI/MMF-based GVHD prophylaxis	37 (100)	0	NA
Median $CD34^+$ cell dose, $\times 10^6$/kg (range)	.1 (.1-.5)	4.0 (1.1-10.0)	<.001
Median follow-up, yr	4	2.6	

Values are n (%) unless otherwise defined. MDS indicates myelodysplastic syndrome; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; CML, chronic myeloid leukemia; CLL, chronic lymphocytic leukemia; KPS, Karnofsky Performance Score; MAC, myeloablative conditioning; NMA, nonmyeloablative; CNI, calcineurin inhibitors; MMF, mycophenolate mofetil.

Table 2
Graft Acquisition Costs and 100-Day Hospital Charges

Charges	dUCBT(n = 37)	Haplo-HCT (n = 49)	P
Graft acquisition charges ($1000)			<.001*
Median (range)	88 (42-135)	35 (7-69)	
Mean ± SD	88 ± 14	35 ± 14	
Missing	0	2	
Outpatient charges ($1000)			.22*
Median (range)	64 (0-219)	74 (0-361)	
Mean ± SD	64 ± 49	80 ± 68	
Missing	0	2	
Outpatient charges per day ($1000)			.27*
Median (range)	.6 (.0-2.2)	.7 (.0-3.6)	
Mean ± SD	.7 ± .5	.8 ± .7	
Missing	0	2	
Inpatient charges ($1000)			.38*
Median (range)	448 (169-1324)	419 (146-1429)	
Mean ± SD	531 ± 266	497 ± 298	
Missing	0	2	
Inpatient charges per day ($1000)			.21*
Median (range)	5.1 (1.7-242.3)	4.2 (1.5-52.4)	
Mean ± SD	13.4 ± 39.1	7.4 ± 8.6	
Missing	0	2	
Total charges (inpatient + outpatients + graft acquisition) ($1000)			.11*
Median (range)	605 (318-1407)	562 (285-1479)	
Mean ± SD	684 ± 259	612 ± 281	
Missing	0	2	
Total charges per day (inpatient + outpatients + graft acquisition) ($1000)			.07*
Median (range)	6.7 (3.2-325.5)	5.8 (2.8-55.6)	
Mean ± SD	17.5 ± 52.4	8.7 ± 8.7	
Missing	0	2	
Day 100 total charges (inpatient + outpatients + graft acquisition) among patients who survived 100 days post-HCT ($1000)			.02*
Median (range)	595 (318-1108)	515 (285-1258)	
Mean ± SD	641 ± 186	540 ± 213	
Missing/deceased	11	12	

SD indicates standard deviation.
* Wilcoxon rank-sum test.

weight and 4×10^6/kg body weight, respectively ($P < .001$). Median follow-up of survivors was 4 years in the dUCBT group and 2.6 years in the haplo-HCT group.

Graft Acquisition Cost and Hospital Charges

The median graft acquisition charges for dUCB and haplo grafts were $88,000 (range, $42,000 to $135,000) and $35,000 (range, $7000 to $69,000), respectively ($P < .001$) (Table 2, Figure 1A). The 100-day outpatient charges submitted to the payers were similar for dUCB versus haploHCT (median $64,000 versus $74,000; $P = .22$) as were the 100-day inpatient charges (median $448,000 versus $419,000, $P = .38$) (Table 2, Figure 1B-D). The median total 100-day charges (inpatient plus outpatient plus graft acquisition) were $605,000 (range, $318,000 to $1,407,000) for the dUCBT group and $562,000 (range, $285,000 to $1,479,000) for the haplo-HCT group ($P = .11$).

Early deaths may have variably affected the median charges for the 2 groups; therefore, to provide an equitable cost comparison between the 2 groups we also evaluated charges excluding deaths in the first 100 days post-HCT. After limiting

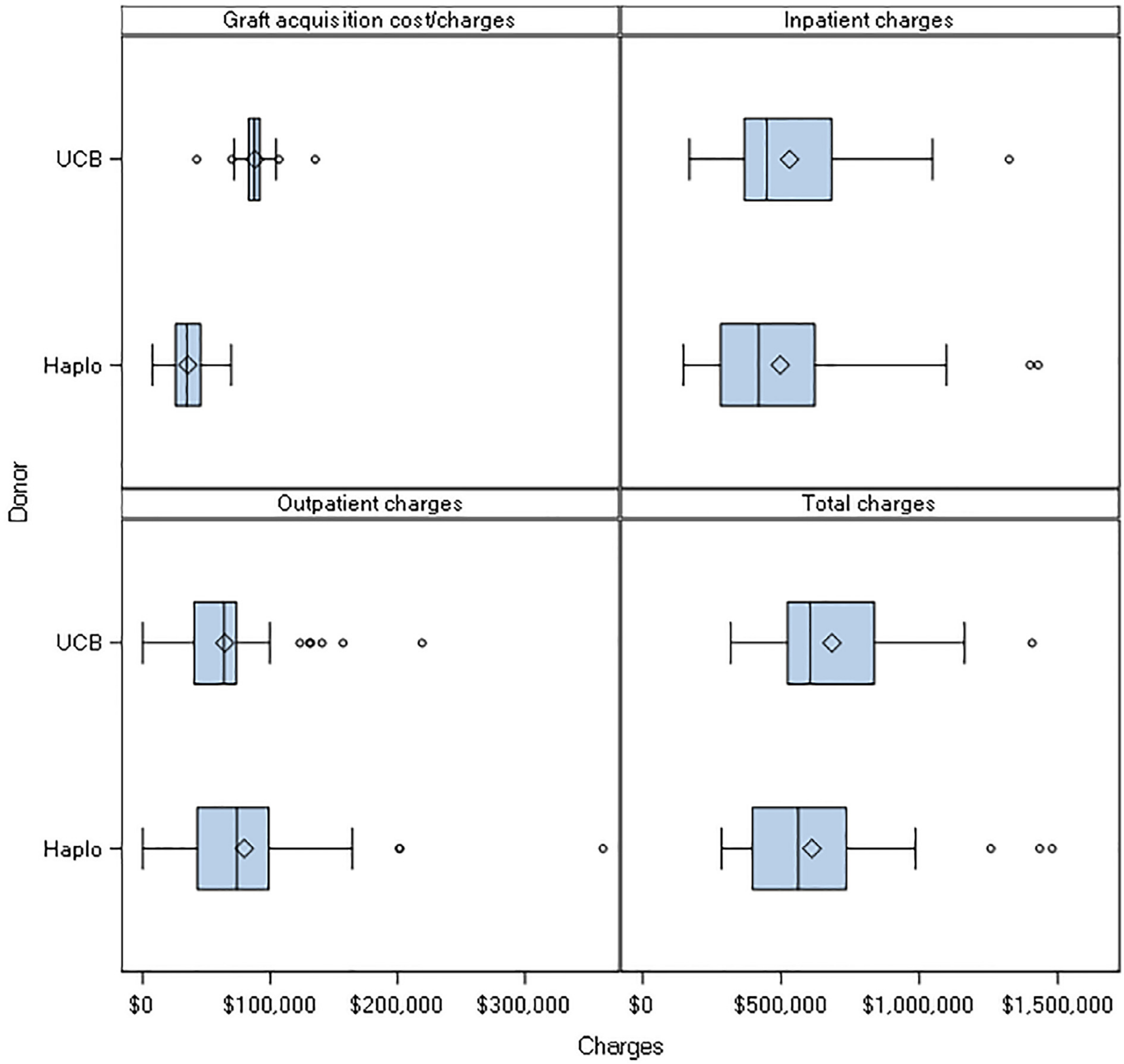

Figure 1. A 100-day cost analysis comparison between dUCBT and haplo-HCT for (A) graft acquisition costs, (B) outpatient hospital charges, (C) inpatient hospital charges, and (D) total hospital charges.

the analysis to subset of patients alive at day +100, there was a significant difference in the 100-day total charges favoring haplo-HCT (median, $595,000 versus $515,000, P = .02).

The multivariable regression analysis considering age, Karnofsky Performance Score, HCT-CI, prior autologous HCT, conditioning intensity, DRI, and number of days alive as covariates revealed that those receiving myeloablative conditioning had a 41% higher 100-day inpatient (P = .004) and 25% higher total charges (P = .01) over those receiving RIC. For both total and inpatient charges a significant interaction between graft source and DRI was observed: For patients with high-risk DRI haplo-HCT had 63% higher 100-day inpatient charges over dUCBT (P = .02), whereas for patients with low or undetermined DRI haplo-HCT was associated with 35% reduction in the total cost (P = .02). Figure 2 illustrates this interaction and the estimated effect of days alive on total charges; the effect on inpatient charges is not shown because it was similar. For simplicity, all nonsignificant predictors were omitted for Figure 2. The fitted model showed that days alive has a nonmonotone effect on the expected charges: Patients alive at day +100 had lower costs than patients who die shortly before that time. The trend toward lower costs for dUCBTs among high-risk patients and the reversal of the effect for low-risk patients is also evident both for the observed and fitted values.

100-Day Transplant Outcomes

The cumulative incidence of neutrophil recovery in dUCBT and haplo-HCT groups by day +30 was 65% (95% confidence interval [CI], 47% to 78%) and 84% (95% CI, 69% to 92%) and by day +60 was 84% (95% CI, 66% to 93%) and 86% (95% CI, 71% to 93%), respectively (P = .25). The cumulative incidence of platelet engraftment in dUCBT and haplo-HCT groups by day +60 was 73% (95% CI, 55% to 85%) and 74% (95% CI, 58% to 84%), respectively (P = .12). Table 3 describes 100-day post-HCT outcomes. During the index hospitalization more cases of viral infections per individual patient were observed after haplo-HCT (35%) compared with dUCBT (8%, P = .004). No difference was noted in the incidence of bacterial and fungal infections

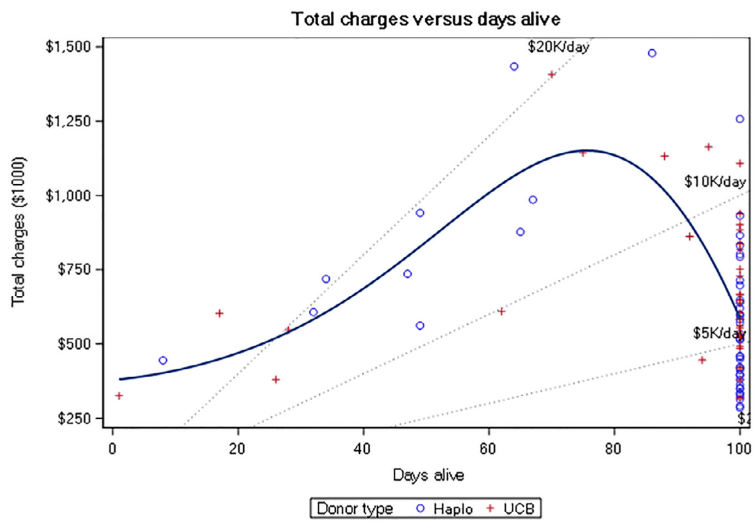

Figure 2. Interaction between total charges (y-axis) by days alive (x-axis) for haplo-HCT and dUCBT.

Table 3
100-Day Post-Transplant Outcomes

Post-Transplant Outcomes by Day +100	dUCBT(n = 37)	Haplo-HCT (n = 49)	*P*
Neutrophil engraftment*			.25
By day +30, % (95% CI)	64.9 (46.7-78.2)	83.7 (69.3-91.7)	
By day +60, % (95% CI)	83.8 (65.9-92.8)	85.7 (71.4-93.2)	
Platelet engraftment by day +60, % (95% CI)*	73 (54.9-84.8)	73.5 (58.3-83.8)	.12
Infections during index admission			
All infections	15 (40.5)	29 (59.2)	.09
Bacterial	13 (35.1)	22 (44.9)	.36
Viral	3 (8.1)	17 (34.7)	.004
Fungal	1 (2.7)	1 (2)	1.00
Acute GVHD by day +100*			
Grades II-IV	6 (16.2)	8 (16.3)	.99
Grades III-IV	1 (2.7)	2 (4.1)	1.00
Median index stay for patients discharged alive, days (range)	28 (12-57) (n = 32)	26.5 (20-64) (n = 42)	.73
Median 100-day hospital-free days (range)			
All patients	61 (0-92)	69 (0-86)	.42
Patients surviving until day +100†	70.5 (4-92)	74 (11-86)	.32
30-day readmission after discharge from index admission	18 (56.3)	19 (45.2)	.35
Inpatient mortality during index admission	5 (13.5)	7 (14.3)	.92
100-day mortality	11 (29.7)	11 (22.4)	.44
100-day OS‡	70.3 (52.8-82.3)	77.6 (63.1-86.9)	.48
100-day PFS‡	62.2 (44.6-75.6)	65.3 (50.3-76.8)	.75
100-day relapse*	18.9 (8.2-33)	20.4 (10.4-32.7)	.90
100-day NRM*	18.9 (8.2-33)	14.3 (6.2-25.6)	.59

Values are n (%) unless otherwise defined.
* Cumulative incidence calculated, *P* value by Gray's test.
† n = 11 in dUCBT, n = 12 in haplo-HCT.
‡ Based on Kaplan-Meier estimate, *P* value by log-rank test.

during this period between the 2 groups. The cumulative incidence of grades II to IV and grades III to IV acute GVHD was similar in the 2 groups (Table 3). Median length of stay during the index admission in the dUCBT and haplo-HCT groups was 28 and 26.5 days, respectively (P = .73), for patients who were discharged to outpatient care. Similarly, no significant difference was noted in 100-day hospital-free days (ie, number of days spent as outpatient in the first 100 days after HCT) between the groups (Table 3). A similar 30-day readmission rate was seen after the index discharge in dUCBT (56%) and haplo-HCT (45%) groups (P = .35). Mortality rate during the index admission and 100-day mortality in dUCBT and haplo-HCT groups were 13.5% and 14.3% (P = .92) and 30% and 22% (P = .44), respectively.

Survival Outcomes

The 100-day cumulative incidence of disease relapse (Figure 3A) in dUCBT and haplo-HCT groups was 18.9% (95% CI, 8.2% to 33%) and 20.4% (95% CI, 10.4% to 32.7%), respectively (P = .9). The corresponding 100-day NRM (Figure 3B) was 18.9% (95% CI, 8.2% to 33%) and 14.3% (95% CI, 6.2% to 25.6%), respectively (P = .59). The 100-day OS was 70.3% (95% CI, 52.8% to 82.3%) and 77.6% (95% CI, 63.1% to 86.9%) in dUCBT and haplo-HCT groups, respectively. The 100-day PFS was 62.2% (95% CI, 44.6% to 75.6%) and 65.3% (95% CI, 50.3% to 76.8%) in dUCBT and haplo-HCT groups, respectively. We performed multivariable analysis using Cox regression (OS, PFS) and Fine-Gray models (NRM, relapse) showing that OS, PFS, and NRM were significantly inferior with dUCBT compared with haplo-HCT (hazard ratio, 3.13, 2.22, and 5.54, respectively; Table 4). There was no significant interaction between the type of HCT and other covariates on multivariable analysis. By day +100 there were 11 deaths each in the dUCBT and haplo-HCT groups, respectively (Supplementary Table 1).

DISCUSSION

Healthcare costs are increasingly a major determinant of healthcare policy. Recipients of allo-HCT represent a unique cohort of patients with significantly high risk of cytopenias, infections, GVHD, electrolyte imbalances, and end-organ toxicities that require prolonged hospitalization, frequent outpatient

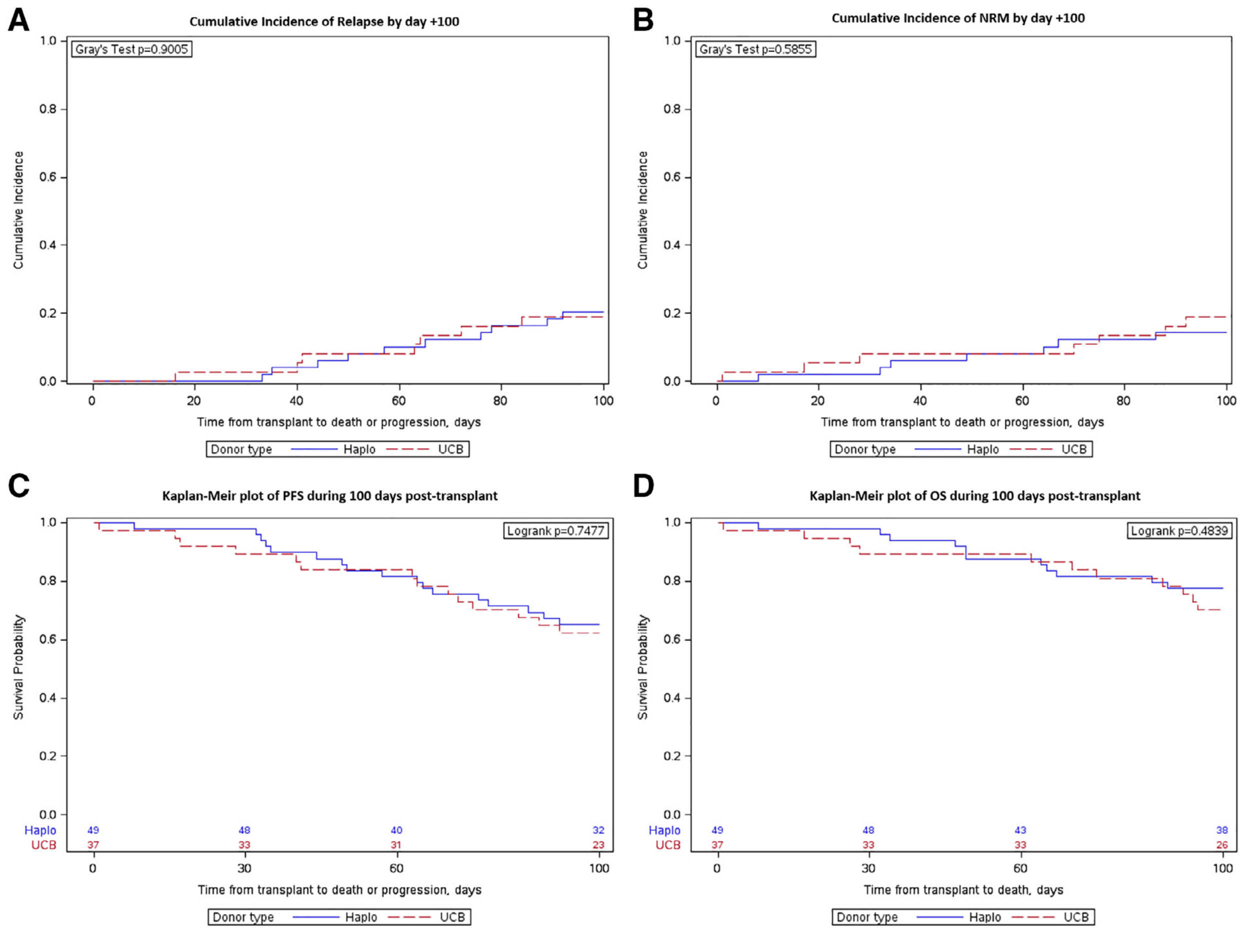

Figure 3. Outcomes after haplo-HCT versus dUCBT. (A) Cumulative incidence of relapse by day +100 post-transplant. (B) Cumulative incidence of NRM by day +100 post-transplant. (C) Kaplan-Meier plot of PFS during 100 days post-transplant. (D) Kaplan-Meier plot of OS during 100 days post-transplant.

follow-up, and increased readmission rates, all of which can potentially escalate healthcare costs [33,34]. In this analysis we compared certain elements of the healthcare costs, limited to the first 100 days of allo-HCT, between 2 alternative donor allo-HCTs, namely dUCBT and haplo-HCT, at 2 US transplant centers in different states, with each center contributing data on only 1 type of transplant. We selected the first 100 days as the time period of interest for the study considering higher morbidity and mortality risk during this period in both types of HCT, as a result of complications such as regimen-related toxicity, delayed or poor count recovery, infections, and acute GVHD.

The graft acquisition cost was significantly lower for haplo-HCT compared with dUCB product. The cost of obtaining the haplo donor grafts was a mean $53,000 lower than dUCB graft. This would effectively translate into a reduction of greater than $1 million in hospital charges (and subsequent healthcare system cost savings) for every 20 haplo-HCT (over dUCBT), assuming the mean graft acquisition charge gap between the 2 donor sources is consistent across transplant centers. Considering that 45% of haplo-HCT recipients received bone marrow product with a higher mean graft acquisition charge ($37,526 versus $27,743 for the peripheral blood product), the cost saving could be even higher with the nearly universal adoption of peripheral blood haplo graft source (as far as graft costs are concerned). This cost saving in the long term, however, could be offset by higher risk of cytokines release syndrome and acute and chronic GVHD with peripheral blood haplo-HCT [35-37]. Of note, the inpatient and total (combined inpatient plus outpatient plus graft acquisition) charges in the first 100 days were similar between the 2 groups. Because mortality in the first 100 days was numerically higher in dUCBT cohort (24% in haplo-HCT versus 30% in dUCBT) and such patients could be associated with higher inpatient charges, we performed a cost analysis restricted to day +100 survivors: Significantly higher total charges were associated with dUCBT (versus haplo-HCT) by a mean value of $101,000. The lack of significant difference in 100-day mortality, length of hospital stay during index admission, and 100-day hospitalization-free days (Table 2) do not provide a simple explanation for the higher total cost of dUCBT among 100-day survivors. We can speculate that the higher cost attribution with dUCBT is linked to greater risk of nonrelapse morbidity and mortality, in addition to the greater cost of graft acquisition and use of ATG [38].

Examination of early post-HCT outcomes with dUCBT and haplo-HCT revealed that haplo-HCT was associated more frequent viral infections, but no significant difference was noted in neutrophil and platelet recovery, day +100 cumulative incidence of acute GVHD, and frequency of fungal and bacterial infections. Surrogates of cost-effectiveness such as length of stay during index admission, 30-day readmission rates, hospital-free days, and mortality were also similar between the dUCBT and haplo-HCT groups within 100 days after HCT. The similar inpatient and outpatient facility charges reported also likely reflect the similar early post-HCT outcomes.

Although similar day +100 NRM and survival was noted between dUCBT and haplo-HCT, by multivariate analysis

Table 4
Multivariate Cox Regression Analysis

Outcome	Hazard Ratio	95% CI	*P*
OS			
dUCBT vs. Haplo-HCT (ref.)	3.13	1.51-6.49	.002
DRI			.54
Intermediate vs. high (ref.)	.68	.33-1.43	.31
Low/NA vs. high (ref.)	.66	.27-1.62	.36
KPS < 90 vs. ≥90 (ref.)	1.61	.82-3.14	.16
HCT-CI < 3 vs. ≥3 (ref.)	.38	.19-.78	.008
RIC/NMA vs. MAC (ref.)	1.01	.46-2.23	.98
Prior auto-HCT vs. no prior auto-HCT (ref.)	.93	.39-2.20	.86
Age at HCT (per 10 years)	1.02	.79-1.32	.86
PFS			
dUCBT vs. Haplo-HCT (ref.)	2.22	1.13-4.37	.02
DRI			.48
Intermediate vs. high (ref.)	.65	.32-1.33	.24
Low/NA vs. high (ref.)	.69	.29-1.64	.40
KPS < 90 vs. ≥90 (ref.)	1.30	.71-2.41	.39
HCT-CI < 3 vs. ≥3 (ref.)	.47	.25-.88	.02
RIC/NMA vs. MAC (ref.)	1.10	.51-2.36	.81
Prior auto-HCT vs. no prior auto-HCT (ref.)	1.38	.64-2.98	.41
Age at HCT (per 10 years)	1.00	.79-1.27	.99
Relapse			
dUCBT vs. Haplo-HCT (ref.)	.79	.34-1.82	.58
DRI			.18
Intermediate vs. high (ref.)	.47	.19-1.15	.10
Low/NA vs. high (ref.)	1.03	.36-2.95	.95
KPS < 90 vs. ≥90 (ref.)	.87	.41-1.85	.72
HCT-CI < 3 vs. ≥3 (ref.)	1.05	.46-2.39	.91
RIC/NMA vs. MAC (ref.)	2.16	.57-8.24	.26
Prior auto-HCT vs. no prior auto-HCT (ref.)	2.44	1.03-5.76	.04
Age at HCT (per 10 years)	.84	.62-1.14	.26
NRM			
dUCBT vs. Haplo-HCT (ref.)	5.54	1.72-17.77	.004
DRI			.45
Intermediate vs. high (ref.)	1.69	.48-5.93	.41
Low/NA vs. high (ref.)	.93	.24-3.63	.92
KPS < 90 vs. ≥90 (ref.)	1.98	.77-5.13	.16
HCT-CI < 3 vs. ≥3 (ref.)	.29	.13-.67	.004
RIC/NMA vs. MAC (ref.)	.53	.19-1.46	.22
Prior auto-HCT vs. no prior auto-HCT (ref.)	.35	.06-1.96	.23
Age at HCT (per 10 years)	1.14	.78-1.67	.50
Total 100-day charges			
Age at HCT	.98	.92-1.04	.50
KPS < 90 vs. ≥90 (ref.)	1.06	.91-1.23	.48
HCT-CI < 3 vs. ≥3 (ref.)	1.02	.87-1.21	.78
Prior auto-HCT vs. no prior auto-HCT (ref.)	.99	.81-1.22	.93
RIC/NMA vs. MAC (ref.)	1.26	1.05-1.51	.02
DRI = high vs. intermediate (ref.) for dUCB	.85	.63-1.15	.28
	1.11	.87-1.42	.39

(*continued*)

Table 4 (*Continued*)

Outcome	Hazard Ratio	95% CI	*P*
DRI = low/NA vs. intermediate (ref.) for dUCB			
Haplo vs. dUCB (ref.) for DRI = high	1.35	.98-1.87	.07
Haplo vs. dUCB (ref.) for DRI = intermediate	.87	.71-1.07	.19
Haplo vs. dUCB (ref.) for DRI = low/NA	.70	.48-1.02	.06
Haplo vs. dUCB (ref.) for DRI = intermediate	.87	.71-1.07	.19
100-day Inpatient charges			
Age at HCT (per 10 years)	.97	.90-1.05	.48
KPS < 90 vs. ≥90 (ref.)	1.02	.84-1.24	.86
HCT-CI < 3 vs. ≥3 (ref.)	1.01	.81-1.24	.95
Prior auto-HCT vs. no prior auto-HCT (ref.)	.97	.75-1.27	.85
RIC/NMA vs. MAC (ref.)	1.42	1.12-1.80	.005
DRI = high vs. intermediate (ref.)	.78	.53-1.15	.21
DRI = low/NA vs. intermediate (ref.) for dUCB	1.20	.88-1.64	.25
DRI = high vs. intermediate (ref.) for dUCB	1.70	1.12-2.59	.01
Haplo vs. dUCB (ref.) for DRI = low/NA	.70	.43-1.13	.14
Haplo vs. dUCB (ref.) for DRI = intermediate	.87	.66-1.13	.29

auto indicates autologous; NA, Not applicable.

dUCBT was associated with a higher NRM. It is possible that the NRM of the dUCBT group is due to most patients receiving ATG (78% versus 0%) as part of their conditioning regimen. [39,40]. Also, by multivariate analysis, compared with dUCBT, haplo-HCT was associated with better survival (PFS and OS) outcomes, likely because of the previously noted association with NRM. This discrepancy could be a center effect, possibly impacted by treatment policies, and caution is warranted in generalizing these results.

A recent single-institution report comparing cost-effectiveness of haplo-HCT with unrelated HCT in patients > 55 years reported that haplo-HCT was approximately €50,000 cheaper than unrelated donor allo-HCT with a median follow-up of 2 years [41]. This study included cost analysis of long-term follow-up including costs of treatment for relapse after HCT. In contrast, in our study the cost analysis was limited to the first 100 days of HCT to ascertain and compare the early transplant-related costs. The ancillary, cost-effectiveness analysis of ongoing BMT CTN 1101 study (NCT 01597778) will report prospectively captured data to compare long-term costs associated with dUCBT and haplo-HCT [21].

Inpatient and outpatient charges were used as a cost metric in our study instead of actual reimbursement from payers and is a limitation of this analysis. Outpatient prescription drug costs were not included in the cost estimates, given the wide variability noted in insurance prescription coverage and patient copays, and this is another limitation of the study. In addition, our analysis does not take into account out-of-pocket expenses, caregiver costs, cost of travel and lodging, and indirect costs related to lost earnings [21], and these must be kept into perspective while interpreting our data. Other limitations of this study include its retrospective nature, small sample size, and center-specific outcomes, which may diminish the generalizability of results. It is likely that post-transplant outcomes including infections, GVHD, and end-organ dysfunction beyond the first 100 days can influence the long-term costs, which unfortunately is beyond the scope of this study. We acknowledge that the analysis may be biased by the fact that 2 types of transplant were performed at 2 separate transplant centers. There may be a wide disparity in charges between the hospitals affiliated with the 2 transplant programs. To address this variation of charges, we adjusted for the potential variability in those charges by using fiscal year 2018 hospital-specific wage index (CMS) [28]. In addition, we controlled costs for inflation as well [27]. Because of the differential pricing strategies in the hospitals/institutions across the country, there may be variability in the charges that may have affected the results of this study, despite the CMS adjustment. Notably, there was no significant difference in charges between haplo-HCT and dUCBT without such adjustments (data not shown). Although an incremental cost-effective ratio analysis would be ideal to assess the cost-effectiveness over a period of time for the 2 transplant strategies, it was deemed beyond the scope for this study, with only outcomes up to day +100 as the period of interest.

In summary, this analysis of hospital and outpatient charges suggests that although acquiring a haplo donor graft is a less expensive donor option compared with dUCB graft, the 100-day charges do not differ significantly between the 2. Although per-patient charges were similar between the 2 graft sources in the early post-transplant period, the lower upfront cost of graft acquisition and the lower 100-day charges associated with haplo-HCT may be a consideration in alternative donor selection, especially in resource-limited scenarios. It remains to be confirmed in a prospective setting if survival outcomes differ between dUCBT and haplo-HCT. The results of the BMT CTN 1101 study (NCT 01597778) will be critical in answering this key clinical question.

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SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at https://doi.org/10.1016/j.bbmt.2019.03.013.

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