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OBM Transplantation

Research Article

Umbilical Cord Blood as an Alternate Donor Sources for High Risk Elderly Patients Undergoing Allogeneic Stem Cell Transplantation for Hematological Malignancies

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Academic Editor: Martin Guimond

Special Issue: Allogeneic Stem Cell Transplantation

OBM Transplantation
2021, volume 5, issue 1
doi:10.21926/obm.transplant.2101136

Received: November 04, 2020
Accepted: February 02, 2020
Published: February 07, 2020

Abstract

Allogeneic stem cell transplantation remains the only curative option for many hematological malignancies. Umbilical cord blood (UCB) is an alternate donor source with potentially increased morbidity in elderly patients. We evaluated outcomes in alternate donor sources, prior to the initiation of haploidentical transplantation at our institution, of matched unrelated donor (MUD) and UCB in elderly patients (mean age 64, range 60-75). One hundred and eighty-four patients were included (MRD: 57; MUD: 69; UCB: 58). There was no difference in acute or chronic graft versus host disease among donor sources (all $p > .05$). In this high-risk population, 128 (70%) had

either a high disease risk index or high (>2) comorbidity index. Median progression free survival (PFS) was lowest among UCB (5.5 months; 95% CI 2.8-9.4) and MUD (5.6 months; 95% CI 3.7-17.7) as compared to MRD (18.3 months; 95% CI 8.4-64.8). On multivariable analysis, the rate of mortality was higher for UCB than MRD patients (1.88, 95% CI 1.04 – 3.37), but there was no difference between UCB and MUD (p = .61) or between MUD and MRD (p = .25). Conclusions were similar for PFS. Our experience shows that even in this high-risk elderly cohort, UCB continues to be a viable alternate donor source.

Keywords
Leukemia; allogeneic; cord blood

1. Introduction

Allogeneic stem cell transplantation (Allo-SCT) is an effective treatment modality for high risk and advanced hematological malignancies [1, 2]. Of the 19,570 new cases of acute myeloid leukemia between 2011 and 2015, 17% were in persons aged 55 to 64 years and 24% in those 65-74 years [3]. Therefore, the role of Allo-SCT is of increasing value in the elderly population. With reduced intensity conditioning/non-myeloablative (RIC/NMA) regimens elderly and less fit patients are undergoing transplantation with lower non relapse mortality (NRM) and acceptable engraftment [4-6].

Approximately one third of patients will have a suitable HLA-matched sibling donor (MRD) and thus more matched unrelated (MUD) and alternate donors are being utilized [7]. Many retrospective and registry studies have shown comparable outcomes among MUD, umbilical cord (UCB), and haploidentical donors (Haplo) amongst elderly patients [8-10] and cord blood transplants can be safe even amongst those in their 70s [11]. However, elderly cohorts are frequently defined as young as 50 with larger cohorts of more elderly patients lacking. We hypothesized that the transplant-related outcomes of elderly patients undergoing UCB transplant for hematological malignancies are comparable to those receiving MUD transplants as an alternate donor source in those without an available MRD. Per our institutional algorithm, our preferred donor source among patients without an available MRD is a MUD followed by UCB. The primary objective of our study is to compare the overall survival of elderly transplant patients over the age of 60 based on donor type.

2. Subjects and Methods

2.1 Study Design and Definitions

Data was collected prospectively and validated retrospectively on patients aged 60 years or greater who underwent Allo-SCT for hematological malignancies at our institution from January 1st 2005 through May 1st, 2016. The following information was collected: Age, gender, donor source (MRD, MUD, and UCB), HCT-CI scores as per Sorror et al. [12], type of conditioning regimen (myeloablative vs non-myeloablative), median days to neutrophil and platelet engraftment, graft versus host disease

prophylactic regimen, use of anti-thymocyte globulin (ATG), recipient and donor CMV status, incidence and grade of aGVHD and cGVHD, and disease risk index (DRI) per Armand et al [13]. Neutrophil engraftment was defined as an absolute neutrophil count greater than or equal to 0.5 x 10^9/L for 3 consecutive days. Platelet engraftment was defined as a platelet count greater than 20 x 10^9/L for 3 consecutive days without transfusion support. Donor chimerism was evaluated per institutional protocol on day 30 (peripheral blood only) and day 100 (peripheral blood and bone marrow) post-transplant and was not lineage specific. Acute GVHD (aGVHD) was graded based on established criteria [14, 15] and chronic GVHD (cGVHD) was scaled based on the National Institutes of Health Consensus Development Projects Criteria [16].

The primary endpoint assessed was overall survival based on donor source. Overall survival was defined as survival from date of transplantation to death from any cause or last follow up. Secondary endpoints analyzed were progression free survival (PFS) by donor source, risk of relapse by donor source, cumulative incidence of aGVHD grades II-IV and III-IV, cumulative incidence of moderate to severe cGVHD, days to neutrophil and platelet engraftment, and donor chimerism.

2.2 Donor Selection, HLA Typing, Preparative Regimen and Immunosuppression

When MRD was not available, our standard of practice for donor selection during this time prioritized MUD over UCB. Therefore, UCB units are only selected when no MUD are available. All MRD were at least 8/8 HLA allele matched (HLA-A, HLA-B, HLA-C, HLA-DRB1 loci, HLA-DQ). MUD were HLA-A, B, C, and DRB1 allele matched and HLA-DPB1 permissive match. UCB grafts were any 4/6, 5/6, and 6/6 matches with HLA-A and HLA-B at the antigen level and DRB1 at the allele level. Conditioning regimen was decided by physician preference. Myeloablative (MA) conditioning regimens included primarily total body irradiation (TBI) based (12 Gy) plus cyclophosphamide (CY) 60mg/kg per day x 2, while non-TBI based regimens were variable but commonly either BuCy (IV Busulfan at 3.2 mg/kg x 4 days with cyclophosphamide 60 mg/kg per day for 2 consecutive days) or BuPent (IV Busulfan 1.6mg/kg Q12 hours for 8 doses with Pentostatin 4 mg/m2 daily for two doses). NMA regimens were variable (see supplementary material). Use of anti-thymocyte globulin (ATG, rabbit) as part of conditioning regimens per institutional protocol was restricted to patients not treated with conventional chemotherapy within three months of transplant.

All patients received dual agent GVHD prophylaxis with continuous infusion of tacrolimus initiated on day -2 at a dose of 0.03 mg/kg/d with the goal of maintaining a level of 10-15 ng/ml. Patients who underwent MRD or MUD transplants also received methotrexate intravenously at a dose of 5mg/m^2 on days +1, +3, and +6 but withheld in the event of grade IV mucositis or if CrCl was less than 10 ml/min on the day of planned administration. Patients who received UCB transplants were prescribed mycophenolate mofetil starting day +1 and continued through day 60. Supportive care including antibacterial, antifungal, and antiviral prophylaxis followed institutional protocols.

2.3 Statistics

Patient demographics are presented as valid counts and proportions stratified by transplant source. Pearson chi-square tests were used to test for an association between transplant source and patient

sex, disease category, conditioning regimen, use of ATG, and CMV risk. Kruskal Wallis tests were used to test the distributions of disease risk, HCT-CI risk, days to engraftment, days to platelet engraftment, age, number of previous chemotherapies, and months from diagnosis to transplant by transplant source. When overall variability among these three cohorts was detected, post-hoc pairwise comparisons were conducted using the Dwass, Steel, and Critchlow-Flinger method [17-19].

Univariable binary logistic regression models were used to estimate the odds of an aGVHD grade of II-IV as a function of age, sex, disease category, count of previous chemotherapies, disease risk, HCT-CI risk, CMV status, use of ATG, conditioning regimen, and transplant source. A similar approach was used to estimate the odds of an aGVHD grade of III-IV and moderate-severe cGVHD grade. In these models, expected frequencies were monitored and, when these values were sparse, exact logistic regression models were used to estimate the odds ratio and its confidence interval. An exact binary logistic regression model was used to estimate the odds of complete donor chimerism as a function of patients' transplant source. For age and count of previous chemotherapies, the linearity assumption for the logistic regression model was assessed using a Hosmer and Lemeshow goodness of fit test.

Finally, univariable and multivariable Cox proportional hazards models were used to estimate the risk of progression or death as a function of the patient characteristics described above. The multivariable model estimated the risk of progression or death as a function of patients' transplant source while controlling for age and count of prior chemotherapies; these covariates were selected because of their significance on univariable analysis. A similar approach was used to model the risk of mortality from any cause. A traditional Kaplan-Meier method was used to estimate the median survival times for each transplant source, while a reverse Kaplan-Meier method was used to estimate follow-up time for each transplant source [20]. Overall survival was defined as survival from time of transplant to death or last follow-up. Multiple pairwise comparisons were adjusted using a Sidak correction to control the Type 1 error rate. All analyses were completed using SAS version 9.4 (Cary, NC).

3. Results

3.1 Patient and Transplant Characteristics

Our cohort included 184 patients (i.e., 58 UCB, 70 MUD, and 56 MRD). Their mean ages (standard deviations) were: MRD = 63.50 (2.91), MUD = 64.60 (3.35), and UCB = 65.19 (3.80); patients in the MRD cohort were nominally lower in age than those in the UCB cohort ($p = .02$). This was a high-risk patient population with 52%, 60%, and 54% having a high DRI among UCB, MUD, and MRD patients, respectively. Further, the incidence of a high DRI *or* high HCT-CI was 60%, 77%, and 70% for UCB, MUD, and MRD patients, respectively. Patient and transplant characteristics for these three groups are shown in Table 1. Of note, more non-myeloablative conditioning regimens were utilized in UCB (74%) than MRD (29%; $p < .001$) or MUD recipients (40%; $p = .001$). TBI based conditioning was also higher for those in the UCB (71%) rather than MRD (41%; $p = .005$) and MUD (34%; $p < .001$) cohorts. The median (range) number of prior chemotherapies were: MRD 2 (0 – 6), MUD 2 (0 – 7), and UCB 3 (1 – 11). The median (interquartile range) months from diagnosis to transplant were: UCB = 14.1 (7.3 – 40.4) MUD = 14.5 (6.9 – 45.2); and MRD = 9.4 (4.6 – 37.0). In this sample, the distribution of months from diagnosis

to transplant were comparable among these three cohorts (p = .12). Overall, patients in the UCB cohort received more prior chemotherapies than those in the MRD cohort (p = .01), but there was no significant difference between patients in the UCB and MUD cohorts (p = .19) or between those in the MRD and MUD cohorts (p = .52). A higher than expected 18 (31%) of the UCB units were CMV positive. Otherwise, transplant characteristics were well balanced among the three groups.

Table 1 Patient demographics by transplant source.

		Transplant Source				
		UCB (n = 58)	**MUD (n = 70)**	**MRD (n = 56)**	**Total (N = 184)**	**Overall *p***
Sex	**Male**	29 (50%)	38 (54%)	37 (66%)	104 (57%)	.20
	Female	29 (50%)	32 (46%)	19 (34%)	80 (44%)	
Disease Category	**AML**	29 (50%)	28 (40%)	14 (25%)	71 (39%)	.07
	MDS	11 (19%)	16 (23%)	18 (32%)	45 (25%)	
	NHL	12 (21%)	11 (16%)	9 (16%)	32 (17%)	
	Other	6 (10%)	15 (21%)	15 (27%)	36 (20%)	
Disease Risk (N = 172)	**Low**	7 (15%)	9 (13%)	16 (29%)	32 (19%)	.41
	Intermediate	15 (33%)	19 (27%)	10 (18%)	44 (26%)	
	High	24 (52%)	42 (60%)	30 (54%)	96 (56%)	
HCT-CI Risk	**Low Risk**	5 (9%)	14 (20%)	10 (18%)	29 (16%)	.94
	Intermediate Risk	32 (55%)	25 (36%)	24 (43%)	81 (44%)	
	High Risk	21 (36%)	31 (44%)	22 (39%)	74 (40%)	
Conditioning	**NMA**	43 (74%)	28 (40%)	16 (29%)	87 (47%)	<.001
	MA	15 (26%)	42 (60%)	40 (71%)	97 (53%)	
Use of ATG	**No**	41 (72%)	53 (76%)	46 (82%)	140 (77%)	.43
	Yes	16 (28%)	17 (24%)	10 (18%)	43 (24%)	
CMV Risk	**Both Negative**	19 (34%)	20 (29%)	24 (44%)	63 (35%)	.26
	Only Recipient Positive	19 (34%)	23 (33%)	8 (15%)	50 (28%)	
	Only Donor Positive	6 (11%)	7 (10%)	6 (11%)	19 (11%)	
	Both Positive	12 (21%)	19 (28%)	16 (30%)	47 (26%)	
TBI Conditioning	**No**	17 (29%)	46 (66%)	33 (59%)	96 (52%)	<.001
	Yes	41 (71%)	24 (34%)	23 (41%)	88 (48%)	

Note: AML: acute myeloma leukemia. MDS: myelodysplastic syndrome. NHL: non-hodgkins lymphoma. NMA: non-myeloablative. MA: myeloablative. HCT-CI: hematopoietic cell transplantation-specific comorbidity. ATG: anti-thymocyte globulin. CMV: cytomegalovirus. UCB: umbilical cord blood. MUD: matched unrelated donor. MRD: matched related donor.

3.2 Engraftment, Chimerism, and GVHD

The median (range) days to neutrophil (ANC) engraftment were: MRD 13 (9 – 20), MUD 13 (range 10 – 28), and UCB 14 (7 – 45). UCB transplants had a longer time to engraftment than MUD transplants (p = .01) though no other pairwise comparisons were significant. The median (range) days to platelet engraftment were: MRD 21 (10 – 45), MUD 19 (0 – 127), and UCB 35 (5 – 89). As with ANC, patients with a UCB transplant source had a longer duration to platelet engraftment than both MRD (p < .001) and MUD (p < .001). However, UCB donors sustained donor chimerism and were 7.36 (95% CI: 1.54 – 70.95; p=.01) and 5.74 (95% CI: 1.15 – 56.36; p=.03) times more likely to have complete donor chimerism at day 100 as compared to MRD and MUD recipients, respectively. In this entire cohort of patients, there were only two cases of engraftment failure and both occurred in the UCB group.

Incidence of acute GVHD did not differ by donor source. Among UCB, MUD, and MRD recipients, the incidence of grade II-IV aGVHD was 35%, 39%, and 26%, respectively. The incidence of grade III-IV aGVHD for these three groups was 12%, 17%, and 18%, respectively. On univariable analysis, males were about 2.03 (95% CI: 1.07 – 3.85) times more likely than females to have an aGVHD grade of II-IV (p = .03), and patients who did not receive ATG were nominally more likely to have aGVHD grade of III-IV (OR = 2.33, 95% CI: 1.001 – 5.42; p = .0498). In this sample, no other patient characteristics were associated with an aGVHD (Table 2). Overall, the incidence of moderate or severe cGVHD was similar among donor sources (overall p = .99). Moderate or severe cGVHD was seen in 40% of UCB, 42% of MUD, and 41% of MRD. No patient characteristics were significantly associated with moderate or severe cGVHD in this sample (Table 2).

Table 2 Odds of aGVHD grade II-IV, aGVHD III-IV, and cGVHD as a function of patient characteristics.

	aGVHD Grade II-IV		**III-IV**		**Moderate or severe cGVHD**	
	OR (95% CI)	***p***	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***
Age (per year increase)	1.07 (0.98 - 1.17)	.16	1.07 (0.96 - 1.2)	.20	0.91 (0.76 - 1.09)	.29
Male	2.03 (1.07 - 3.85)	.03	1.31 (0.58 - 2.96)	.51	0.99 (0.37 - 2.62)	.98
Disease Category[b]		.64[a]		.29[a]		.49
Prior chemo (per count increase)	1.13 (0.94 - 1.37)	.21	1.12 (0.89 - 1.41)	.35	1.07 (0.77 - 1.47)	.70
Disease Risk		.16[a]		.27[a]		.93[a]
High vs Intermediate	0.69 (0.28 - 1.68)	.68	0.58 (0.19 - 1.75)	.56	0.84 (0.19 - 3.65)	.99
High vs Low	1.87 (0.60 - 5.87)	.47	1.65 (0.33 - 8.21)	.84	0.81 (0.20 - 3.35)	.98

Intermediate vs Low	2.71 (0.78 - 9.50)	.16	2.84 (0.53 - 15.31)	.36	0.97 (0.19 - 5.08)	.99
HCT-CI Risk		.16[a]		.50[a]		.10[a]
High vs Intermediate	1.29 (0.56 - 2.95)	.85	1.51 (0.51 - 4.49)	.74	3.03 (0.79 - 11.66)	.14
High vs Low	0.55 (0.19 - 1.58)	.44	0.82 (0.22 - 3.04)	.98	3.07 (0.55 - 17.13)	.32
Intermediate vs Low	0.42 (0.15 - 1.23)	.16	0.54 (0.14 - 2.10)	.63	1.01 (0.18 - 5.69)	.99
CMV Risk Status[c]		.48[a]		.40[a]		.23
Use of ATG	1.57 (0.78 - 3.17)	.21	2.33 (1.001 - 5.42)	.049	1.55 (0.44 - 5.41)	.50
Condition: MA vs NMA	0.63 (0.34 - 1.17)	.14	0.95 (0.43 - 2.11)	.91	0.72 (0.27 - 1.93)	.51
Transplant Source		.38[a]		.65[a]		.99[a]
MUD vs MRD	1.72 (0.68 - 4.34)	.42	0.95 (0.31 - 2.93)	.99	1.02 (0.28 - 3.71)	.99
UCB vs MRD	1.44 (0.54 - 3.82)	.75	0.63 (0.18 - 2.25)	.77	0.95 (0.17 - 5.49)	.99
UCB vs MUD	0.84 (0.35 - 2.03)	.95	0.66 (0.20 - 2.26)	.81	0.93 (0.15 - 5.83)	.99

Note: Confidence limits and significance values have been adjusted for inflated Type 1 error using a Sidak correction for disease risk, HCT-CI risk, and transplant source. aOverall Type-3 significance test. aGVHD = Acute graft-versus host disease. cGVHD = Chronic graft-versus-host disease. HCT-CI: Hematopoietic cell transplantation-specific comorbidity. CMV = Cytomegalovirus. ATG: anti-thymocyte globulin. NMA: non-myeloablative. MA: myeloablative. UCB: umbilical cord blood. MUD: matched unrelated donor. MRD: matched related donor. AML: acute myeloma leukemia. MDS: myelodysplastic syndrome. NHL: non-hodgkins lymphoma. bDisease categories includes all possible pairwise comparisons among patients with AML, MDS, NHL, and other. cCMV risk includes all possible pairwise comparisons among donors and recipients where both the donor and recipient were negative, only the recipient was positive, only the donor was positive, or both the donor and recipient were positive.

3.3 Relapse and Overall Survival

The median follow-up times were 56.4 (95% CI: 50.7 – 63.2) months for UCB, 45.5 (95% CI: 31.1 – 72.8) months for MUD, and 76.9 (95% CI: 51.9 – 90.7) months MRD transplants. Overall median progression free survival (PFS) for the entire cohort was 8.1 (95% CI 5.5-12.0) months, while it was 5.5 (95% CI 2.8-9.4), 5.6 (95% CI 3.7-17.7), and 18.3 (95% CI 8.4-64.8) months for UCB, MUD, and MRD recipients, respectively (Figure 1). On univariable analysis, increasing age was nominally associated with an increased rate of relapse (HR = 1.06, 95% CI: 1.01 – 1.12; p = .02) as was an increasing count of prior

chemotherapy interventions (HR = 1.13, 95% CI: 1.02 – 1.25; p = .02). Compared to MRD patients, those in the UCB cohort were more likely to relapse (HR = 2.15, 95% CI: 1.26 – 3.66; p = .002). Neither the disease risk index nor HCT-CI score were associated with relapse on univariable analyses (Table 3). However, after controlling for age and the count of previous chemotherapies, patients with a UCB transplant source remained significantly more likely to relapse than those receiving an MRD source (HR = 1.79, 95% CI: 1.02 – 3.17; p = .04), but there was no difference between UCB and MUD donor sources (HR=1.36, 95% CI: 0.82 – 2.25; p = .39)(Table 4).

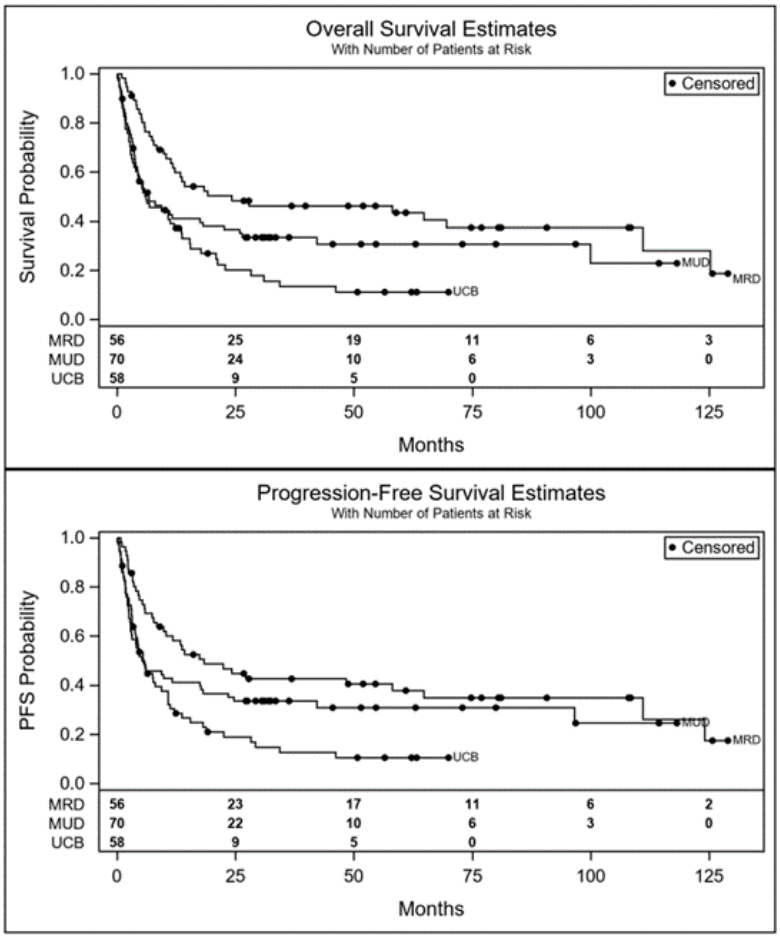

Figure 1 Overall and progression-free survival estimates by donor source.

Table 3 Rates of relapse or mortality.

	Unadjusted		**Adjusted**	
	Hazard Ratio (95% CI)	***p***	**Hazard Ratio (95% CI)**	***p***
Age (per year increase)	1.06 (1.01 - 1.12)	.02	1.05 (0.997 – 1.11)	.064
Sex: Male vs Female	0.92 (0.65 - 1.30)	.63		

Disease Category		.64[a]		
AML vs MDS	1.17 (0.65 - 2.10)	.98		
AML vs NHL	0.93 (0.49 - 1.77)	.99		
AML vs Other	1.27 (0.67 - 2.43)	.91		
MDS vs NHL	0.80 (0.39 - 1.62)	.95		
MDS vs Other	1.09 (0.54 - 2.22)	.98		
NHL vs Other	1.37 (0.64 - 2.94)	.85		
Prior chemo (per count increase)	1.13 (1.02 - 1.25)	.02	1.09 (0.98 – 1.21)	.10
Disease Risk		.35[a]		
High vs Intermediate	1.18 (0.70 - 1.97)	.84		
High vs Low	1.40 (0.79 - 2.47)	.41		
Intermediate vs Low	1.19 (0.62 - 2.28)	.89		
HCT-CI Risk		.57[a]		
High Risk vs Intermediate Risk	1.17 (0.74 - 1.82)	.80		
High Risk vs Low Risk	1.28 (0.68 - 2.42)	.73		
Intermediate Risk vs Low Risk	1.10 (0.58 - 2.07)	.98		
Use of ATG: Yes vs No	1.04 (0.69 - 1.55)	.86		
Condition Regimen: MA vs NMA	0.99 (0.70 - 1.39)	.94		
Transplant Source		.003[a]		.048[a]
MUD vs MRD	1.43 (0.84 - 2.44)	.29	1.32 (0.77 – 2.27)	.53
UCB vs MRD	2.15 (1.26 - 3.66)	.002	1.79 (1.02 – 3.17)	.04
UCB vs MUD	1.50 (0.92 - 2.45)	.14	1.36 (0.82 – 2.25)	.39

Note: For the adjusted estimates, valid N = 184 (with 133 events). Confidence limits and significance values have been adjusted for inflated Type 1 error using a Sidak correction for disease category, disease risk, HCT-CI risk, and transplant source. [a]Overall Type-3 significance test. AML: acute myeloma leukemia. MDS: myelodysplastic syndrome. NHL: non-hodgkins lymphoma. HCT-CI: hematopoietic cell transplantation-specific comorbidity. ATG: anti-thymocyte globulin. NMA: non-myeloablative. MA: myeloablative. UCB: umbilical cord blood. MUD: matched unrelated donor. MRD: matched related donor.

Table 4 Rates of mortality from any cause.

	Unadjusted		**Adjusted**	
	Hazard Ratio (95% CI)	***p***	**Hazard Ratio (95% CI)**	***p***
Age (per year increase)	1.06 (1.01 – 1.12)	.02	1.05 (0.996 – 1.11)	.07
Sex: Male vs Female	0.85 (0.60 – 1.21)	.37		

Disease Category		.81[a]		
AML vs MDS	1.09 (0.60 – 1.97)	.99		
AML vs NHL	0.95 (0.49 – 1.85)	.99		
AML vs Other	1.23 (0.64 – 2.38)	.96		
MDS vs NHL	0.87 (0.43 – 1.80)	.99		
MDS vs Other	1.13 (0.55 – 2.32)	.99		
NHL vs Other	1.29 (0.59 – 2.82)	.95		
Prior chemo (per count increase)	1.13 (1.02 – 1.25)	.02	1.09 (0.98 – 1.22)	.10
Disease Risk		.20[a]		
High vs Intermediate	1.17 (0.70 – 1.98)	.85		
High vs Low	1.56 (0.86 – 2.83)	.21		
Intermediate vs Low	1.33 (0.67 – 2.62)	.69		
HCT-CI Risk		.42[a]		
High Risk vs Intermediate Risk	1.23 (0.78 – 1.95)	.62		
High Risk vs Low Risk	1.33 (0.70 – 2.52)	.63		
Intermediate Risk vs Low Risk	1.08 (0.57 – 2.04)	.99		
Use of ATG: Yes vs No	1.12 (0.74 – 1.68)	.60		
Condition Regimen: MA vs NMA	0.94 (0.66 – 1.34)	.74		
Transplant Source		.002[a]		.04[a]
MUD vs MRD	1.60 (0.93 – 2.76)	.11	1.48 (0.85 – 2.57)	.25
UCB vs MRD	2.26 (1.31 – 3.91)	.001	1.88 (1.04 – 3.37)	.03
UCB vs MUD	1.41 (0.86 – 2.31)	.26	1.27 (0.76 – 2.12)	.61

Note: For the adjusted estimates, valid N = 184 (with 129 events). Confidence limits and significance values have been adjusted for inflated Type 1 error using a Sidak correction for disease category, disease risk, HCT-CI risk, and transplant source. [a]Overall Type-3 significance test. AML: acute myeloma leukemia. MDS: myelodysplastic syndrome. NHL: non-hodgkins lymphoma. HCT-CI: hematopoietic cell transplantation-specific comorbidity. ATG: anti-thymocyte globulin. NMA: non-myeloablative. MA: myeloablative. UCB: umbilical cord blood. MUD: matched unrelated donor. MRD: matched related donor.

Median OS was 10.8 (95% CI 6.6 – 14.3) months for the entire cohort and 6.6 (3.6 – 12.0), 6.1 (95% CI 3.9 – 18.2), and 24.3 (95% CI 11.3 – 111.0) months for UCB, MUD, and MRD recipients, respectively (Figure 1). One and 3-year NRM for UCB, MUD, and MRD were 47% and 56%, 51% and 55%, and 29% and 39% respectively. OS was quite poor among all three donor types in patients with both a high DRI *and* high HCT-CI (n = 42) making allo-HCT potentially prohibitive in this patient population. In these 42 patients, the 100 day and 2-year OS rates were: 80% and 10% for UCB, 58% and 17% for MUD, and 69% and 17% for MRD, respectively.

On univariable analysis, increasing age was associated with an increased rate of mortality (HR = 1.06, 95% CI: 1.01 – 1.12; p =.02) as was an increasing count of prior chemotherapy interventions (HR = 1.13, 95% CI: 1.02 – 1.25; p =.02). Compared to those with an MRD transplant source, patients with a UCB source were more likely to die (HR = 2.26, 95% CI: 1.31 – 3.91; p = .001); there was no significant

difference in mortality rates between those with a MUD versus MRD transplant source (HR = 1.60, 95% CI: 0.93 – 2.76; p = .11) or between those with a UCB vs MUD transplant source (HR=1.41, 95% CI: 0.86 – 2.31; p = .26)(Table 4). Controlling for patients' age and count of prior chemotherapies, patients with a UCB transplant source remained significantly more likely to die when compared to those receiving an MRD transplant source (HR = 1.88, 95% CI: 1.04 – 3.37; p = .03) (Table 4).

4. Discussion

This analysis aimed to show that UCB and MUD donor transplants are comparable alternate donors in elderly patients over the age of 60. In this patient population, elderly UCB and MUD transplant recipients had similar outcomes, but both inferior to MRD which should remain the gold standard for donor source in this high-risk elderly group. The results of this analysis are significant because, at best, approximately one third of elderly patients will have an MRD thus the critical importance of alternate donor sources [21]. Our data show that UCB can be considered as an alternate donor source in this elderly and importantly very high-risk cohort as 52% of our UCB recipients had a high disease risk index and 91% had an intermediate to high risk HCT-CI score.

The high NRM and poor survival in general in this patient cohort suggests caution when evaluating these patients for allo-SCT. Well-designed clinical trials aimed at both reducing relapse risk and morbidity following Allo-SCT are needed. One unexpected finding in this cohort was the increased risk of relapse in the UCB group. This is possibly due to more non-myeloablative conditioning regimens utilized in UCB transplant recipients. Our outcomes are on par with the reported literature in this patient population. Armand et al. showed that those with a very high DRI have only a 23% 2-year OS (13) and the Minnesota group recently showed those with an HCT-CI score greater than or equal to 3 and a high DRI do quite poor with a two-year OS of just 34% and specifically among UCB patients (32%) [22]. Importantly, the Minnesota data looked at a younger patient cohort at 50 years of age and above.

Data from Memorial Sloan Kettering Cancer center shows that despite efforts from the National Marrow Donor Program to increase minority involvement and registry size, minimal improvement has been made with 14% of African Americans not having either an available 7/8 or 8/8 MUD or UCB graft in their larger experience [23]. With ethnic diversity increasing in North America, MUD donor sources will not be as readily available increasing the reliance on both haploidentical and UCB grafts. In institutions like ours that serve a primarily minority population of low socioeconomic status, the problem is compounded. Haplos are hampered by falling family sizes and UCB the ever-growing ethnic diversity. However, both have the inherent advantage of allowing for more HLA-disparity. As to whether Haplo or UCB is the preferred donor source remains a debate. Preliminary results of the CTN-1101 randomized trial comparing double UCB to Haplo appear to favor Haplo transplants. The trial did not meet the expected 15% difference in 2-year PFS but overall survival and NRM favored the haplo group [24].

The safety and long-term viability of UCB transplants in elderly patients has been demonstrated. In the most elderly cohort, Sandhu et al. reported in a single institution experience a two-year NRM of 20% and 3-year relapse rate of 30% in patients greater than 70 years of age undergoing UCB Allo-SCT for AML/MDS [11]. In a multi-institution experience, Latour et al. evaluated an "elderly" cohort of those

greater than 50 years of age undergoing Allo-SCT with UCB for AML in CR1 showing an acceptable 3-year NRM of 33% comparable to a concurrent MRD and MUD cohort [10]. The Latour study was a lower risk population with only 34% of patients having a high DRI and HCT-CI score was not reported. Larger registry studies have shown similar outcomes although again with elderly being defined as young as 50 and lower risk cohorts overall in regards to DRI and HCT-CI [25, 26].

Infectious complications remain a significant challenge for patients undergoing UCB. Thirty-eight percent of the deaths in our cohort of UCB recipients could be directly attributed to infectious complications. Various methodologies of cord blood expansion have been evaluated with the goal to speed engraftment and reduce infectious complications [27-29]. Our institution has been involved in such attempts including both arlecortemcel-L [30] and nicotinamide [31]. Thus far, the experience has shown faster engraftment, delayed hospitalization costs, and decreased early infections but importantly a lack of mature randomized data [32]. An alternate approach to improving infectious outcomes in UCB donors is to improve T-cell engraftment which is known to be poor and delayed in UCB recipients [33]. We are actively investigating transplantation with UCB cells concurrently with an ex-vivo expanded population of thymic seeding cells to improve efficacy and accelerate T-cell engraftment with promising early in-vitro results.

In conclusion, UCB remains a viable alternate donor stem cell source for elderly patients over the age of 60. Our experience along with others reported in the literature should give pause however when assessing the highest risk elderly patients with both a high HCT-CI and high DRI. Novel methods in addition to cord blood expansion are needed to reduce NRM and in particular infectious complications in UCB recipients. While our data support that MRD is the gold standard donor source in this patient population, improving outcomes for all alternate donor sources addressing each's inherent challenges is critical to ensuring all patients who are candidates for Allo-SCT are offered this potentially curative therapy.

Author Contributions

Patrick Hagen: Data collection and manuscript writing; William Adams: Data collection and manuscript writing; Shruti Singh: Data collection and manuscript writing; Shuai Qin: Data collection and manuscript writing; Loredana Campo: Data collection and manuscript writing; Stephanie Tsai: Manuscript writing; Nasheed Hossain: Manuscript writing; Scott E Smith: Manuscript writing; Patrick J Stiff: Manuscript writing.

Competing Interests

The authors have declared that no competing interests exist.

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