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ORIGINAL ARTICLE

MDS disease characteristics, not donor source, predict hematopoietic stem cell transplant outcomes

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Myelodysplastic syndrome (MDS) is a heterogeneous group of hematological malignancies with considerably variable prognoses and curable only with hematopoietic cell transplantation (HCT). Few studies comparing MDS HCT outcomes between sibling and umbilical cord blood (UCB) donors exist. Using the University of Minnesota Blood and Marrow Transplant (BMT) database, we retrospectively analyzed HCT outcomes among 89 MDS patients undergoing either sibling or double UCB HCT in 2000–2013. We observed similar survival, relapse and non-relapse mortality between sibling and UCB donor sources. Relapse was increased in those with monosomal karyotype ($P = 0.04$) and with reduced intensity conditioning ($P < 0.01$). In summary, our data highlight similar MDS HCT outcomes regardless of donor source and support the use of UCB as an alternative donor when a sibling is unavailable.

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INTRODUCTION

Myelodysplastic syndromes (MDS) are a complex and heterogeneous group of clonal hematopoietic stem cell disorders for which the only known cure is allogeneic stem cell transplantation (hematopoietic cell transplantation (HCT)).[1,2] Numerous publications have identified the importance of prognostic stratification[3,4] for HCT timing in both myeloablative (MA) and reduced intensity conditioning (RIC) settings[5,6] and have identified the importance of cytogenetic risk stratification in HCT outcomes.[7–9] Donor source also has a key role in MDS transplant outcomes. A recent CIBMTR (Center for International Bone Marrow Transplant Registry) analysis comparing the outcomes of adult MDS patients undergoing a sibling or adult matched unrelated donor (MUD) HCT receiving MA or RIC highlighted diminished survival, increased non-relapse mortality (NRM) and increased incidence of severe acute GVHD (aGVHD) with unrelated donors compared with siblings.[10] In contrast, a European Group for Blood and Marrow Transplantation (EBMT) analysis of 1333 MDS patients aged >50 years receiving either a sibling or MUD donor transplant revealed similar 4-year survival at approximately 31% with advanced disease at HCT the primary variable impacting survival but increased NRM with unrelated donor source.[11]

Although comparisons of sibling and unrelated donor transplants in MDS are readily available, the literature comparing sibling donors and umbilical cord blood (UCB) is less developed. Registry data provide the largest cohorts of patients for such outcome analyses comparing alternative donor HCT in MDS. Robin *et al.*[12] presented the first large report evaluating outcomes of UCB HCTs in MDS on behalf of Eurocord and EBMT comparing patients with either MDS ($n = 39$) or AML secondary to MDS ($n = 69$) undergoing MA or RIC UCB. They reported 2-year overall survival (OS) of 34%, 2 year disease-free survival (DFS) of 30% and 2-year incidence of relapse of 21%. Severe aGVHD grades III–IV occurred in approximately 11%, 2-year chronic GVHD (cGVHD) was 42% and NRM was high at 49%. NRM was adversely influenced by MA conditioning and a longer time from diagnosis to transplantation. Although this study was the first to report a larger cohort of patients undergoing UCB transplant for MDS, the number of patients with true MDS in this cohort was small and the patient population and transplant approaches were heterogeneous owing to the retrospective registry nature of the study.

To further describe MDS transplant outcomes comparing sibling and UCB donor sources in a more homogenous patient population with consistent conditioning platforms, we retrospectively analyzed HCT outcomes among MDS patients undergoing either sibling or double UCB allogeneic stem cell transplant at our institution.

METHODS

Data source

Through the University of Minnesota Blood Marrow Transplant (BMT) database, we identified 89 consecutive adult patients (⩾18 years of age) with MDS who underwent MA or RIC allogeneic HCT using either sibling or double UCB donors from 2000 to 2013.

Data collection

All patients were treated on protocols reviewed and approved by the University of Minnesota Institutional Review Board and all participating subjects provided informed consent according to the principles of the Declaration of Helsinki before proceeding to transplant. Data were prospectively collected in the institutional BMT database.

End points and definitions

The primary end point was an outcome comparison between recipients of sibling or UCB donor sources in the context of MDS disease characteristics. Secondary end points included NRM, relapse and DFS. Disease relapse was defined as any recurrence of hematological, morphological or cytogenetic markers consistent with disease prior to transplant.

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Diagnostic specimens were reviewed by institutional hematopathologists and classified by the 2008 World Health Organization (WHO) MDS criteria.[13] Therapy-related MDS was defined clinically as MDS following exposure to alkylating agents, topoisomerase II inhibitors or radiotherapy. Blast percentage categories ($\leqslant$2%, $>$2–$<$5, 5–10 and $>$10) were chosen to distinguish patients with deeper levels of remission ($\leqslant$2%, $>$2–$<$5) from those with a greater burden of persistent disease (5–10%, $>$10) as defined in the Revised International Prognostic Scoring System (R-IPSS).[4] Standard G-banding techniques were used for cytogenetic analysis; two authors (BT, MD) independently scored all available cytogenetic analyses by R-IPSS cytogenetic stratification with discrepancies resolved by consensus review.[4] Disease status was described as untreated MDS, CR, treated—responsive and treated—resistant. Monosomal karyotype (MK) was defined as the presence of two monosomies or one monosomy with an additional chromosomal abnormality.[14]

HLA typing, matching and donor selection

Selection of sibling and UCB grafts has been previously reported.[15] HLA-related donors were siblings based on family testing. Filgrastim-mobilized PBSCs were used in sibling transplants. UCB unit nucleated cell dose and matching have been described elsewhere; however, in brief donors were required to be 4-6/6 HLA-matched to the recipient and each other considering HLA A and B at the antigen level and DRB1 at the allele level.[15] Preparative regimens were classified as either MA or RIC by established CIBMTR functional definitions.[16–18]

Treatment

Patients received either MA or RIC conditioning as previously reported.[19,20] Equine ATG (15 mg/kg twice daily for six doses from day −6 through day −4) in the setting of RIC for those UCB transplants who had $\leqslant$1 cycle of multi-agent chemotherapy within 3 months or for related donors with $\leqslant$1 cycle of multi-agent chemotherapy within 6 months prior to HCT.

Supportive care

All patients received supportive care, including blood product support, infection prophylaxis (bacterial, fungal, CMV/herpes simplex virus and *Pneumocystis jiroveci*) and GVHD prophylaxis. For GVHD prophylaxis, the majority of patients received cyclosporine-based regimens (targeting trough levels $>$200 ng/mL) through day +180 with either pulsed methotrexate in MA regimens or mycophenolate mofetil through day +30 with RIC regimens. Filgrastim was administered to all patients through ANC recovery.

Statistical analysis

Disease, patient and transplant characteristics were compared by chi-square test for categorical factors and General Wilcoxon test for continuous factors. Unadjusted OS and DFS was estimated from Kaplan–Meier curves.[21] Unadjusted estimates of NRM were analyzed using cumulative incidence treating relapse as a competing risk. Relapse, engraftment and GVHD were analyzed using cumulative incidence treating non-event mortality as a competing risk.[22]

The primary focus of our analysis was comparing MDS HCT outcomes between matched sibling and double UCB donors. Other factors assessed in regression models included MDS cytogenetic classification (R-IPSS cytogenetic classification, MK absence or presence) conditioning intensity (MA versus RIC ± ATG), age, disease status at transplant (untreated, CR, treated—responsive versus treated—resistant), diagnosis (MDS unspecified/refractory anemia (RA)/RA with ring sideroblasts versus RA with excess blasts 1 and 2 versus RA with multilineage dysplasia RCMD/RA with multilineage dysplasia—ringed sideroblasts), therapy-related MDS (no versus yes), Karnofsky at HCT ($<$90 versus 90–100), hematopoietic cell transplant comorbidity index (HCT-CI) at HCT (low versus intermediate versus high), recipient CMV serostatus (negative versus positive) and bone marrow blasts at transplant ($\leqslant$2% versus 2–4% versus 5–10% versus $>$10%).

Cox regression was used to assess the independent effect of the donor type and MDS cytogenetic classification (R-IPSS cytogenetic classification versus MK) on 5-year OS and DFS.[23] Fine and Gray proportional hazards regression was used to assess the independent effect of donor type and cytogenetic classification (R-IPSS cytogenetic classification versus MK) on NRM, relapse, engraftment and GVHD.[24] Donor type and one MDS cytogenetic classification was used in each model. Other variables that remained statistically significant or confounded the effect of donor type and MDS disease characteristics were included in the models as appropriate. Visual plots and Martingale residuals were used to test against non-proportionality.[25] All reported *P*-values were two-sided. SAS 9.3 (SAS Institute, Cary, NC, USA) and R 3.0.2 (R foundation for Statistical Computing, Vienna, Australia) were used for all statistical analyses.

RESULTS

Patient demographics

Patient disease and transplant characteristics for the 89 patients (median age 55, range 19–72 years) are included in Table 1. Patient age, gender, year of transplant, WHO categorization, disease status at transplant, Karnofsky performance score, HCT-CI, R-IPSS cytogenetics at diagnosis, presence of MK and bone marrow blasts at transplant were similar between sibling and UCB donor sources. A higher percentage of sibling donors underwent MA conditioning (47% versus 11% UCB) and accordingly more frequently used cyclosporine/methotrexate-based GVHD prophylaxis. Median follow-up of survivors was longer for siblings at 7.7 years (range 3–12.1) as compared with 3.3 years (range 3–6.2) for UCB recipients.

OS and DFS

Five-year survival for the entire group was 37%. There was no difference in survival outcomes between donor sources: 5-year survival for sibling donor and UCD recipients were 41% (95% confidence interval (CI) 26–56%) and 33% (95% CI 19–48%) ($P=0.29$), respectively. (Figure 1) Conditioning did not confer a survival difference at 5 years: 39% (95% CI, 20–58%) for MA compared with 40% (95% CI, 25–55%) for RIC with ATG and 30% (95% CI, 11–51%) for RIC without ATG ($P=0.80$) (Table 2).

Post-HCT outcomes were impacted by MDS cytogenetic classification. In univariate analysis, those with MK had inferior 5-year OS at 21% (95% CI, 7–39%) compared with those without at 44% (95% CI, 31–57%) ($P=0.02$). Patients with very-poor-risk cytogenetics defined by the R-IPSS categorization at diagnosis had inferior 5-ear survival at 15% (95% CI, 3–36%) compared with those with good or very good cytogenetics at 62% (95% CI, 42–77%). Those in CR had the best 5-year survival at 80% (95% CI, 20–97%) but no other disease status at HCT impacted survival.

In multiple regression analyses, we evaluated the impact of donor source, one of the two MDS cytogenetic classifications (R-IPSS cytogenetic classification versus MK) and other statistically or clinically significant or confounding variables on 5-year survival. Table 3 describes these findings. Donor source had no impact on OS in multiple regression analysis across MDS cytogenetic classifications. Both MDS cytogenetic classifications predicted OS but the R-IPSS Cytogenetic risk group was most predictive with relative risk (RR) of 3 (95% CI, 1.3–6.6) in the very-poor-risk group ($P=0.05$)

Primary cause of death by donor type was similar for both sibling and UCB HCTs, with disease relapse and infection the two most common causes of death. Graft failure and new malignancy were unique causes of deaths restricted to UCB Table 4.

DFS mirrored OS outcomes at 5 years with DFS of 32% (95% CI, 22–43%). There was no difference in DFS outcomes between donor sources, conditioning intensity, disease status at transplant, therapy-related MDS or CMV status. Multiple regression analysis confirmed similar outcomes between donor sources and impact of WHO classification and R-IPSS cytogenetic risk grouping but less impact of MK.

Relapse and NRM

The majority of relapses occurred by 1 year. The cumulative incidence of relapse at 1 and 2 years was 24% (95% CI, 15–33%)

Table 1. Patient demographics

Variable	*Siblings*	*UCB*	P-*value*
N	45	44	
Age (years); median (range), (IQR)	55 (27–71), (49–62)	58 (19–72), (51–64)	0.48
Age, years			0.75
18–29	2 (4%)	1 (2%)	
30–49	11 (24%)	9 (21%)	
50+	32 (71%)	34 (77%)	
Year of HCT			0.21
2000–2006	19 (42%)	13 (30%)	
2007–2013	26 (58%)	31 (71%)	
Patient gender: male	32 (71%)	28 (64%)	0.45
Conditioning			< 0.01
MA	21 (47%)	5 (11%)	
RIC: with ATG	17 (38%)	27 (61%)	
RIC: without ATG	7 (16%)	12 (27%)	
GVHD prophylaxis			< 0.01
CSA/MMF	23 (51%)	37 (84%)	
CSA/MTX	17 (38%)	1 (2%)	
Other	5 (11%)	6 (14%)	
Diagnosis: WHO			0.28
RA/RARS/MDS unknown	14 (31%)	9 (20%)	
RAEB 1 and 2	19 (42%)	26 (59%)	
RCMD/RCMD-RS	12 (20%)	9 (11%)	
Disease status			0.37
Untreated MDS	19 (42%)	11 (25%)	
CR	2 (4%)	3 (7%)	
Treated—responsive	14 (31%)	19 (43%)	
Treated—resistant	10 (22%)	11 (25%)	
Prior therapy			0.15
No treatment	19 (42%)	11 (25%)	
Induction	10 (22%)	19 (43%)	
HMA	11 (24%)	12 (27%)	
Lenalidomide	5 (11%)	2 (5%)	
Therapy-related MDS, yes	11 (24%)	11 (25%)	0.99
Karnofsky: < 90	9 (20%)	5 (11%)	0.26
HCT-CI			0.47
Low risk	17 (38%)	13 (30%)	
Intermediate	16 (36%)	14 (32%)	
High risk	12 (27%)	17 (39%)	
R-IPSS cytogenetic classification at DX			0.71
Very good	1 (2%)	1 (2%)	
Good	14 (31%)	15 (34%)	
Intermediate	6 (13%)	7 (16%)	
Poor	10 (22%)	13 (30%)	
Very poor	14 (31%)	8 (18%)	
MK at Dx, present	17 (38%)	11 (25%)	0.19
BM blasts at HCT			0.11
⩽2%	29 (64%)	27 (61%)	
3–4%	7 (16%)	13 (30%)	
5–10%	5 (11%)	4 (9%)	
>10%	4 (9%)	0	
Patient CMV: positive	22 (49%)	27 (61%)	0.24
Follow-up, median (IQR)	7.7 years (3.0–12.1)	3.3 years (3.0–6.2)	

Abbreviations: BM = bone marrow; Bu = busulfan; CSA = cyclosporine; Cy = cyclophosphamide; Dx = diagnosis; Flu = fludarabine; HCT = hematopoietic cell transplantation; HCT-CI = hematopoietic cell transplant comorbidity index; HMA = hypomethylating agents; IQR = interquartile range; MA = myeloablative; MDS = myelodysplastic syndrome; MK = monosomal karyotype; MMF = mycophenolate mofetil; MTX = methotrexate; RA = refractory anemia; RAEB = refractory anemia with excess blasts; RARS = refractory anemia with ring sideroblasts; RCMD = refractory anemia with multilineage dysplasia; RCMD-RS = refractory anemia with multilineage dysplasia—ring sideroblasts; RIC = reduced intensity conditioning; R-IPSS = Revised International Prognostic Scoring System; UCB = umbilical cord blood; WHO = World Health Organization. Note: 'GVHD prophylaxis—Other': Sibling: sirolimus/tacrolimus, MTX/ATG/tacrolimus, and CSA/CD34 selection; UCB: sirolimus/MMF.

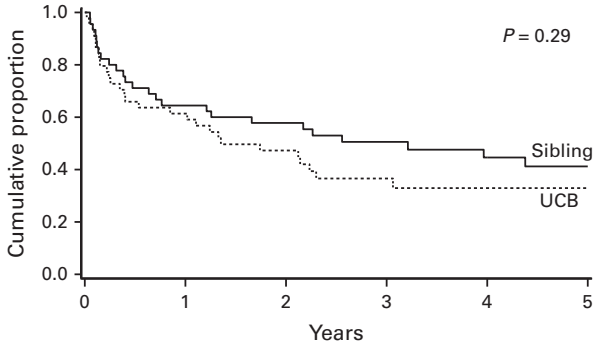

Figure 1. OS by donor type.

and 28% (95% CI, 18–38%) respectively. There was no difference in incidence of relapse at 2 years between donor sources: siblings 27% (95% CI, 13–40%) versus UCB 30% (95% CI, 16–44%). There were lower rates of 2-year relapse with MA conditioning at 12% (95% CI, 0–24%) versus RIC+ATG at 32% (95% CI, 18–46%) versus RIC with no ATG at 42% (95% CI, 19–65%), but this did not reach statistical significance ($P = 0.07$). (Figure 2)

Patients with MK had a higher 2-year incidence of relapse at 39% (95% CI, 21–58%) compared with 24% (95% CI, 13–35%) in those without ($P = 0.03$) (Figure 3). R-IPSS cytogenetic category at diagnosis was less consistent at predicting relapse in our cohort of patients as evident by rates of relapse within R-IPSS cytogenetic subgroups contrary to well-published trends. Disease status at transplant, WHO category, prior treatment, bone marrow blast percentage at transplant or therapy-related MDS did not predict relapse.

In multivariate analysis, we found no difference in risk of relapse with respect to donor source or disease status at transplant. When comparing the different MDS cytogenetic classifications, MK (RR 2.7 (95% CI, 1.0–6.9) $P = 0.04$) most strongly predicted relapse. Regardless of the cytogenetic model used, conditioning intensity consistently and significantly predicted RR with higher risk in the RIC groups.

NRM at day +100 was 18% for the entire cohort and was similar with respect to donor source: 16% (95% CI, 5–26%) for siblings compared with 20% (95% CI, 9–32%) for UCB. Recipients aged ⩽29 years had superior survival with 0% NRM at day +100. Gender, Karnofsky performance score, HCT-CI nor year of transplant impacted NRM. Those with a bone marrow blast percentage >10% had very high NRM of 75% at day +100 (95% CI, 34–100%; $P < 0.01$).

One-year NRM remained relatively low for the entire cohort at 25%. In multivariate analysis, there was no difference in NRM by donor type. Conditioning did impact NRM with lower NMR with RIC compared with MA conditioning.

GVHD

Incidence of aGVHD grades II–IV at day +100 were modest at 38% (95% CI, 28–49%) for the entire cohort and were similar between donor sources. Severe aGVHD grades III–IV at day +100 were 19% overall with an incidence of 27% (95% CI, 14–40%) in siblings and 11% (95% CI, 2–21%) in UCB ($P = 0.09$). There was a higher incidence of severe aGVHD in those with MK at 32% (95% CI, 15–49%) compared with 14% (95% CI, 5–22%) in those without and also a higher incidence in those with >10% blasts at 50% (95% CI, 11–89%). In multiple regression analysis, there was no difference in severe aGVHD grades III–IV by donor source.

The overall incidence of cGVHD at 1 year was 31% (95% CI, 21-42%) for the entire cohort. We did observe a difference in rates of cGVHD based on donor source with a low incidence of 18% (95% CI,

Table 2. Univariate analysis

Patient, disease and HCT variables	N	*5-year OS (95% CI)*	P-*value*	*1-year NRM (95% CI)*	P-*value*	*2-year relapse (95% CI)*	P-*value*	*5-year DFS (95% CI)*	P-*value*
All patients	89	37% (26–47%)		25% (16–34%)		28% (18–38%)		32% (22–43%)	
Age, years			0.15		0.10		0.50		**0.03**
18–29	3	100%		0%		0%		100%	
30–49	20	33% (14–54%)		40% (19–61%)		25% (6–44%)		19% (5–39%)	
⩾50	66	35% (22–47%)		21% (11–31%)		30% (19–42%)		33% (21–46%)	
HCT-CI risk			0.32		0.53		0.13		0.07
Low (0)	30	47% (28–64%)		20% (6–34%)		17% (3–30%)		48% (29–65%)	
Intermediate (1–2)	30	31% (15–48%)		30% (13–47%)		30% (13–47%)		25% (12–42%)	
High (3+)	29	32% (14–51%)		24% (9–40%)		38% (19–57%)		24% (9–42%)	
WHO classification			**<0.01**		0.11		0.74		**<0.01**
RA/RARS/MDS-U	23	38% (19–57%)		26% (8–44%)		26% (8–44%)		34% (16–53%)	
RCMD/RCMD-RS	45	11% (2–29%)		38% (17–59%)		29% (9–48%)		5% (0–20%)	
RAEB 1/2	21	51% (34–65%)		18% (7–29%)		29% (15–43%)		48% (33–62%)	
Percentage of BM blasts at HCT			0.22		**<0.01**		0.69		0.58
⩽2	56	43% (29–56%)		18% (8–28%)		32% (20–45%)		34% (21–48%)	
>2–<5	29	19% (4–42%)		35% (14–56%)		20% (3–37%)		23% (7–44%)	
5–10	9	42% (11–71%)		22% (0–48%)		33% (4–63%)		44% (14–72%)	
>10	4	25% (1–67%)		75% (34–100%)		0% (all patients had died)		25% (1–67%)	
MK			**0.02**		0.52		**0.03**		**0.03**
Yes	28	21% (7–39%)		25% (9–41%)		39% (21–58%)		19% (6–36%)	
No	59	44% (31–57%)		24% (13–35%)		24% (13–35%)		39% (27–52%)	
R-IPSS cytogenetics at Dx			**<0.01**		0.42		**0.01**		**<0.01**
Very good/good	31	62% (42–77%)		16% (3–29%)		23% (8–38%)		57% (38–73%)	
Intermediate	13	15% (2–39%)		23% (1–45%)		54% (24–83%)		0%	
Poor	23	37% (17–56%)		35% (15–54%)		13% (0–26%)		38% (19–57%)	
Very poor	22	15% (3–36%)		27% (9–46%)		36% (16–57%)		13% (3–33%)	
Disease status at HCT			0.36		0.61		0.71		0.40
Untreated MDS	30	36% (18–54%)		30% (14–46%)		33% (16–51%)		25% (11–42%)	
CR	5	80% (20–97%)		20% (0–51%)		20% (0–50%)		60% (13–88%)	
Treated—responsive	33	40% (23–57%)		18% (5–31%)		28% (12–43%)		40% (23–57%)	
Treated—resistant	21	27% (10–47%)		29% (9–48%)		24% (6–42%)		29% (12–48%)	
Donor type			0.29		0.57		0.68		0.60
Sibling	45	41% (26–56%)		22% (10–34%)		27% (13–40%)		34% (20–48%)	
UCB	44	33% (19–48%)		27% (14–41%)		30% (16–44%)		33% (19–47%)	
Conditioning intensity			0.80		0.76		0.07		0.64
MA	26	39% (20–58%)		31% (13–48%)		12% (0–24%)		35% (17–54%)	
RIC with ATG	44	40% (25–55%)		23% (10–35%)		32% (18–46%)		35% (21–49%)	
RIC without ATG	19	30% (11–51%)		21% (3–39%)		41% (19–65%)		26% (10–47%)	
Year of transplant			0.17		0.20		0.33		0.06
2000–2006	32	28% (14–44%)		31% (15–47%)		31% (14–48%)		21% (9–37%)	
2007–2013	57	44% (30–57%)		21% (10–32%)		27% (15–38%)		40% (27–53%)	

Abbreviations: BM = bone marrow; CI = confidence interval; DFS = disease-free survival; Dx = diagnosis; HCT = hematopoietic cell transplantation; HCT-CI = hematopoietic cell transplant comorbidity index; MA = myeloablative; MDS = myelodysplastic syndrome; MDS-U = myelodysplastic syndrome unspecified; MK = monosomal karyotype; NRM = non-relapse mortality; OS = overall survival; RA = refractory anemia; RAEB = refractory anemia with excess blasts; RARS = refractory anemia with ring sideroblasts; RCMD = refractory anemia with multilineage dysplasia; RCMD-RS = refractory anemia with multilineage dysplasia—ring sideroblasts; RIC = reduced intensity conditioning; R-IPSS = Revised International Prognostic Scoring System; UCB = umbilical cord blood; WHO = World Health Organization. Bold entries indicate statistically significant results.

7–30%) in the UCB cohort compared with 44% (95% CI, 28–61%) in the sibling cohort ($P = 0.02$). This finding was confirmed in multivariate analysis (UCB RR 0.3 (95% CI, 0.1–0.7; $P < 0.01$).

DISCUSSION

Outcomes with stem cell transplant for MDS remain variable with the universal goal of identifying the most important predictors of transplant success to yield better patient and donor selection, better pre-HCT therapy selection to improve pre-HCT disease burden and identification of alternative approaches for those with only minimal chance of benefit from transplant. Our data highlighted similar outcomes regardless of sibling or UCB donor source and confirm the ability of well-established cytogenetic classification models to predict post-HCT survival and relapse in our patient population.

Table 3. Multivariate analysis: comparison of donor type and MDS disease characteristic risk groups

	Relative risk (95% CI for outcome of interest)			
	Model with MK		*Model with diagnostic R-IPSS cytogenetic risk group*	
	Donor type	*MK*	*Donor type*	*R-IPSS cytogenetic risk group*
OS	1.7 (1.0–3.1)	1.6 (0.9–2.9)	1.7 (1.0–3.1)	Intermediate: **2.9 (1.1–7.5)** Poor: 1.9 (0.8–4.2) Very poor: **3 (1.3–6.6)** **$P=0.05$**
DFS	1.3 (0.8–2.3)	1.5 (0.9–2.7)	1.3 (0.8–2.3)	Intermediate: 3.6 (1.5–8.9) Poor: 1.6 (0.8–3.5) Very poor: 2.6 (1.2–5.5) $P=<0.01$
NRM	1.7 (0.7–4.1)	0.9 (0.4–2.3)	1.7 (0.8–4.0)	Intermediate: 2.2 (0.6–7.9) Poor: 2.6 (0.9–8.1) Very poor: 1.8 (0.5–6.8)
Relapse	0.7 (0.3–1.5)	**2.7 (1.0–6.9)** **$P=0.04$**	0.8 (0.4–1.8)	Intermediate: 3.3 (1.1–9.5) Poor: 0.6 (0.1–2.4) Very poor: 2.5 (0.8–8.1) **$P=0.03$**

Abbreviations: DFS = disease-free survival; MDS = myelodysplastic syndrome; MK = monosomal karyotype; NRM = non-relapse mortality; OS = overall survival; R-IPSS = Revised International Prognostic Scoring System. Sibling is reference for donor type, very low/low is reference for high/very high in CIBMTR MDS HCT (Center for International Bone Marrow Transplant Registry Myelodysplastic Syndrome Transplant) risk group, 'No' is reference for monosomal karyotype, very low/low is reference for intermediate/high/veryhigh for R-IPSS cytogenetics at diagnosis. Confounding variables for OS and DFS are World Health Organization diagnosis, for relapse are disease status and conditioning. Cells in bold are statistically significant.

Table 4. COD by donor source

COD	*Siblings (deaths = 25)*	*UCB (deaths = 24)*
Graft failure	0	2 (7%)
Infection	6 (24%)	5 (18%)
ARDS	0	1 (4%)
aGVHD	1 (4%)	2 (7%)
cGVHD	1 (4%)	0
Disease	10 (40%)	9 (32%)
Organ failure	2 (8%)	3 (11%)
New malignancy	0	3 (11%)
Hemorrhage	2 (8%)	0
Other/unknown	3 (12%)	3 (11%)

Abbreviations: aGVHD = acute GVHD; ARDS = acute respiratory distress syndrome; cGVHD = chronic GVHD; COD = cause of death; UCB = umbilical cord blood.

Sibling donors remain the donor of choice for patients requiring transplant; however, when siblings are not available controversy exists regarding the next best option. Although comparisons of sibling and unrelated donor transplants in MDS are readily available, the literature investigating UCB is less developed. Our institutional alternative donor HCT research interest has pioneered the field of UCB transplantation. When an urgent HCT is needed and few unrelated donor options are available, our institutional alternative donor choice is an UCB source. Our current data highlight similar outcomes regardless of donor source and are

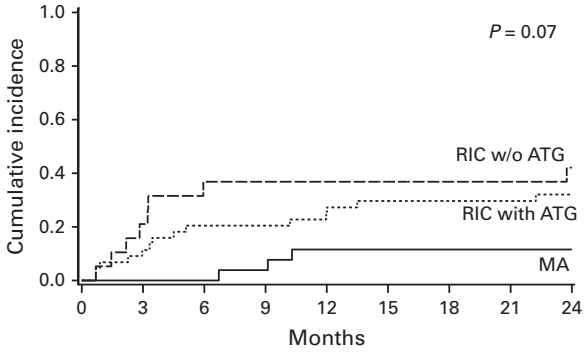

Figure 2. Relapse incidence by conditioning intensity.

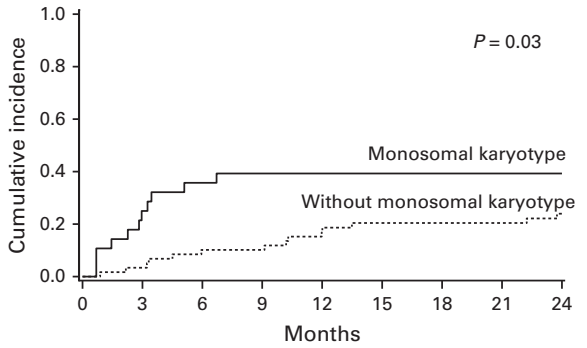

Figure 3. Relapse incidence by MK.

consistent with previous publications from our institution with respect the MDS and AML outcomes.[19,26] To date, the largest MDS UCB outcomes analysis was a recent 2015 Eurocord-EBMT analysis highlighting the outcomes of MDS adults undergoing either UCB ($n=129$) or peripheral blood MUD ($n=502$) RIC HCT. In this analysis, 2-year survival ranged from 30% for UCB to 50% for MUD ($P<0.0001$) with similar relapse incidence across donors (23% MUD to 30% UCB) but increased NRM at 42% for UCB compared with 31% for PB MUD ($P=0.03$). Based on these data, the authors concluded that PB MUD donors were the preferred stem cell source compared with UCB in the absence of a sibling donor.[27] Although the outcomes of this study highlight a much larger 'MDS' patient cohort, it is important to note that 65% of the MDS patients within the entire cohort had progressed to AML prior to transplantation, and of those patients, only 52% had achieved remission prior to transplant. Specifically, within the UCB group 71% had progressed to AML and only 48% had achieved CR prior to transplant. This study is thus limited by the heterogeneity of patients/conditioning regimens/supportive care inherent in a registry study and the small number of true MDS patients not progressing to AML receiving an UCB HCT ($n=37$).[27] Despite these limitations, the analysis importantly highlights surprisingly good outcomes of survival and relapse for such a high-risk group of patients with the majority of the MDS patients progressing to AML, only half in remission, and receiving only RIC. Thus these data suggest that both MUD/UCB RIC transplants can be effective in curing even high-risk MDS/AML patients. Although our study is limited by a relatively small total sample size with shorter follow-up in the UCB cohort, the 44 patients with true MDS undergoing HCT with an UCB donor source represents the largest published population of such patients to date. The experience at the University of Minnesota developing and fine tuning the approach to UCB transplantation (utilizing UCB in the setting of an urgent transplant need with few unrelated donor options and avoiding use in the setting of extensive marrow fibrosis) along with the

consistent conditioning platform and supportive care across all patients likely partially explains these differential outcomes between our study and the EBMT-Eurocord analysis.

Predicting outcomes after HCT remains an ongoing area of intense research in MDS. If we can better identify who will do well, or very poorly, with transplant and what prior therapy optimizes disease burden prior to HCT, then we can improve outcomes for patients and eliminate transplant-related risks for those who are unlikely to benefit. Numerous publications have investigated MDS characteristics that may impact HCT outcomes looking at disease burden based on bone marrow blast percentage at the time of transplant,[1,2,8] R-IPSS cytogenetic risk grouping,[8] MK[7]and cytogenetic disease burden by percentage of cytogenetically abnormal cells,[9] with the general consensus that MK, poor/very-poor R-IPSS cytogenetics, high blast percentage at transplant and high disease burden by percentage of cytogenetically abnormal cells, are adverse predictors of transplant outcomes. Our analysis confirmed the impact of established MDS risk assessments (R-IPSS cytogenetics and MK) on transplant outcomes but small numbers challenge extensive subset analysis.

Relapse was influenced by conditioning intensity with fewer and later relapses in the MA conditioning cohort compared with a higher relapse incidence in the RIC cohort. Interestingly, within the RIC cohort, those not receiving ATG had the highest incidence of relapse. By protocol definition, those who received pre-HCT multi-agent chemotherapy did not require ATG inclusion in the RIC preparative regimen, and thus likely highlights a more advanced MDS patient population. This difference in relapse did not translate into a survival difference between the conditioning intensity cohorts, suggesting that the pace of relapse in MDS disease biology allowed time for additional interventions that prevented death following relapse. Although the recent prospective randomized BMT CTN 0901 trial comparing conditioning intensity in AML and MDS did show increased relapse and a trend toward improved OS in the MA cohort, the study included only a small percentage of MDS patients and thus does not definitively answer the conditioning intensity debate in MDS.[29]

In summary, our data support the use of UCB donors for MDS patients requiring transplant as a viable alternative donor, highlighting comparable outcomes to sibling donors at an experienced center.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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