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Early Hematopoietic Stem Cell Transplant is Associated with Favorable Outcomes in Children with MDS

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Abstract

Background—Although hematopoietic stem cell transplantation (HSCT) is the treatment of choice for childhood myelodysplastic syndrome (MDS), there is no consensus regarding patient or disease characteristics that predict outcomes.

Procedure—We reviewed 37 consecutive pediatric MDS patients who received myeloablative HSCT between 1990 and 2010 at a single center.

Results—Twenty had primary MDS and 17 had secondary MDS. Diagnostic cytogenetics included monosomy 7 (n=21), trisomy 8 (n=7) or normal/other (n=8). According to the modified WHO MDS classification, thirty had refractory cytopenia and 7 had refractory anemia with excess blasts. IPSS scores were: low risk (n=1), intermediate-1 (n=15), and intermediate-2 (n=21). OS and DFS at 10-years in the entire cohort was 53% and 45%. Relapse at 10-years was 26% and 1-year TRM was 25%. In multivariate analysis, factors associated with improved 3-year DFS were not receiving pre-HSCT chemotherapy (RR=0.30, 95% CI 0.10–0.88; p=0.03) and a shorter interval (<140 days) from time of diagnosis to transplant (RR=0.27, 95% CI 0.09–0.80; p=0.02). 3-year DFS in patients who did not receive pre-HSCT chemotherapy and those who had a shorter interval to transplant (n=16) was 80%.

Conclusion—These results suggest that children with MDS should be referred for allogeneic HSCT soon after diagnosis and that pre-HSCT chemotherapy does not appear to improve outcomes.

INTRODUCTION

Myelodysplastic syndrome (MDS) is a clonal disorder of hematopoiesis with variable bone marrow dysplasia and cellularity, progressive cytopenias, and a propensity for transformation to acute myelogenous leukemia (AML) [1]. It is heterogeneous in presentation and rare in children, with distinct features in pediatric patients as compared to adults. These features have impeded the diagnosis, classification, and scientific understanding of this disease in the past [2]. Recently strides have been made toward the classification of pediatric MDS, with new acceptance of minimal diagnostic criteria. Though

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a blurring of clinical categories may still exist, pediatric MDS is understood to be a distinct disease from myeloid leukemia of Down syndrome and juvenile myelomonocytic leukemia (JMML), and is composed of the following subdivisions: refractory cytopenia (RC), refractory anemia with excess blasts (RAEB) and RAEB in transformation (RAEB-T) [3].

Hematopoietic stem cell transplant (HSCT) is the only curative therapy for pediatric MDS, although other therapies have been attempted including immunosuppressive therapy, epigenetic modifying agents, high-dose chemotherapy, and hematopoietic growth factors [4–7]. With continued refinements in HLA-typing, availability of umbilical cord blood and improvements in supportive care management, the availability of HSCT has increased and outcomes have improved. Today, outcomes for unrelated donor HSCT for hematologic diseases are similar to those seen in recipients of HLA matched related donor (MRD) [7–16]. Although an improvement in survival has been reported, treatment related mortality (TRM) and relapse remain the most common causes of death [7,9,12,15,17].

There has been little consensus regarding patient or disease characteristics, or treatment-related factors that may be associated with transplant outcomes for pediatric MDS. This is likely related to small patient samples and challenges in diagnosis and classification of MDS in children. Previously reported prognostic factors have included donor type, French American British (FAB) subtype, bone marrow and peripheral blood blast percentage, time from diagnosis to HSCT, age, cytopenias, trephine biopsy characteristics, and karyotype [12–16,18–20]. The international prognostic scoring system (IPSS), which has effectively correlated disease factors at presentation to outcomes in adults, has been applied to the pediatric population; however, results are of limited value as only BM blasts <5% and platelet count $>100 \times 10^9/L$ were found to successfully predict survival [21]. Worse outcomes have also been observed in patients with secondary MDS, defined as MDS arising either after prior chemotherapy, aplastic anemia or a bone marrow failure syndrome, or familial MDS [17,22].

Because MDS is a rare pediatric disease, the majority of the literature on outcomes and prognostic factors are from registry studies. While of clear value, such studies are limited by heterogeneous treatment and supportive care regimens. In this study we report the results for 37 consecutive pediatric patients with MDS undergoing HSCT at the University of Minnesota to determine whether patient, disease or treatment characteristics can be identified predicting post-HSCT outcomes.

MATERIALS AND METHODS

Study design

We performed a retrospective review of 37 consecutive pediatric patients (<21 years old at diagnosis) who received allogeneic HSCT for MDS between August 1990 and May 2010. All were transplanted on institutional review board approved treatment protocols, and all patients/guardians provided signed informed consent.

Donor selection and HLA typing

Stem cell sources included HLA MRD bone marrow, matched or mismatched unrelated donor (MURD or MMURD) bone marrow, and unrelated umbilical cord blood (UCB). For recipients of UCB, patients and donors were typed for HLA-A and -B at the antigen level and for -DRB1 at the allele level. For recipients of MURD and MMURD, patients and donors had antigen level typing at HLA-A and -B and allele level typing at HLA-DRB1 until June 2005, when testing at the allele level for all loci, including C, was implemented. All HLA matched related donors had antigen level typing at HLA-A, -B, and -DRB1 unless

adequate family typing was not available to determine haplotypes, in which case allele level DNA typing was performed at all loci when available after 2005.

Supportive care

Patients were hospitalized in single rooms ventilated with high-efficiency particulate air filtration systems. Patients at high risk for recurrence of herpes simplex (titer 1:8) received prophylactic acyclovir. Patients at high risk of cytomegalovirus (CMV) reactivation (recipient or donor with a titer 1:8) received prophylactic high-dose acyclovir until day 100. Broad-spectrum antibiotics were administered for fever during aplasia, and antifungals were added for persistent fever unresponsive to antibiotic therapy. All patients received fluconazole for prophylaxis of yeast infections for 100 days, trimethoprim-sulfamethoxazole for prophylaxis of *Pneumocystis (carinii) jiroveci* after engraftment for 12 months after transplantation, and antibiotic prophylaxis (penicillin, gatifloxacin, or levofloxacin) for Gram-positive organisms during the treatment of GVHD.

Endpoints

Study endpoints included neutrophil engraftment, overall survival (OS), disease free survival (DFS), relapse, acute graft-versus-host-disease (aGVHD; grades II-IV and grades III-IV), chronic GVHD (cGVHD), and treatment-related mortality (TRM). Neutrophil engraftment was defined as the first of 3 consecutive days with an absolute neutrophil count (ANC) $> 0.5 \times 10^9/L$. OS was defined as the time from transplant (day 0) until death or last contact. DFS was defined as the time from transplant (day 0) until disease recurrence, death, or last patient contact, whichever came first. Relapse was defined as a morphologic and/or cytogenetic recurrence of MDS after HSCT. Acute GVHD and cGVHD were evaluated and graded according to previously published criteria, with histopathologic confirmation when possible [23,24]. All patients with engraftment were considered evaluable for GVHD. TRM was defined as death in the first 100 days after HSCT for any reason other than relapse.

Statistical Methods

Data on transplant patient characteristics, post-transplantation complications and outcomes were collected prospectively by the Biostatistical Support Group at the University of Minnesota using standardized collection procedures. Patients and disease characteristics were summarized using descriptive statistics. All patients were followed longitudinally until death or last follow up. Kaplan-Meier was used to estimate neutrophil recovery, OS and DFS [25]. Cumulative incidence was used to estimate relapse, TRM, aGVHD, and cGVHD. Statistical comparison of neutrophil engraftment, OS and DFS between groups was completed by the Log-Rank test [26]. The proportional hazards model of Fine and Gray was used to assess the independent factors on relapse, TRM, aGVHD, and cGVHD [27]. Statistical analysis was performed with Statistical Analysis System statistical software version 9.2 (SAS Institute). Groups with value of $p \leq 0.05$ were considered to be statistically different.

RESULTS

Patient and Disease Characteristics

Patient characteristics are summarized in Table I. Twenty patients (54%) had primary (de novo) MDS and 17 (46%) had secondary MDS (4 treatment-related, 8 with preceding idiopathic aplastic anemia, 3 with Schwachman-Diamond syndrome, and 2 familial [defined as MDS occurring in one or more first degree relatives]). Those with juvenile myelomonocytic leukemia, Fanconi anemia, myelodysplasia-related AML and MDS associated with Down Syndrome were excluded. Patients were retrospectively assigned a

modified World Health Organization (WHO) classification and scored according to the International Prognostic Scoring System (IPSS) [3][28]. Thirty patients (81%) had refractory cytopenia (RC) and 7 (19%) had refractory anemia with excess blasts (RAEB) according to the modified WHO MDS classification. The IPSS risk of our patients was as follows: low (n=1), intermediate-1 (Int-1; n=15), intermediate-2 (Int-2; n=21), high (n=0). Seven patients (19%) received pre-HSCT chemotherapy which comprised of AML induction chemotherapy (DCTER regimen n=3, COG AAML0531 n=1, Ara-c/mitoxantrone + FLAG/Ida n=1, unknown n=1) with the exception of one patient who received only *cis*-retinoic acid. No patients received DNA methyltransferase inhibitor (DNAMTi) agents. The decision to use pre-HSCT chemotherapy was at the discretion of the treating physician. Response to the pre-HSCT chemotherapy was mixed – 3 had worsening blasts counts, 2 had stable blast counts and 2 had improved blast counts. There was no correlation between blast count at diagnosis or interval from diagnosis to HSCT and the use of pre-HSCT chemotherapy. All patients were transplanted following myeloablative conditioning (cyclophosphamide/total body irradiation [n=29], cyclophosphamide/fludarabine/total body irradiation [n=6], busulfan/cyclophosphamide [n=1] and busulfan/fludarabine/melphalan [n=1]). Donor sources included UCB (HLA matched [6/6], n=1; HLA mismatched at 1 or 2 loci [4/6 or 5/6], n=8), MRD (n=15), MURD (n=7) and MMURD [5/6] (n=6). Median length of follow-up for survivors was 8 years (range 1–17).

Hematopoietic Recovery and Engraftment

Neutrophil engraftment occurred in 89% (95% CI 77–97%) of patients at a median of 23 days (range, 12–40). Multivariate analysis demonstrated that patients transplanted after 1999 were more likely to engraft by day +42 (RR 2.27, 95% CI 1.06–4.88; p=0.04). There were no other significant predictors of engraftment.

Overall Survival

Overall survival was 70% (95% CI 53–82%) and 53% (95% CI 36–68%) at 1 and 3-years. Survival remains 53% at 10 years. (Figure 1A) Univariate analysis revealed improved 3-year OS in patients transplanted after 1999 (85% vs. 38%, p=0.02), those who had a pre-HSCT blast count of <5% (66% vs. 20%, p=0.01), those who had an MDS classification of RC (61% vs. 17%, p=0.03), those who did not receive pre-HSCT chemotherapy (63% vs. 14%, p<0.01) and those who had a shorter interval from time of diagnosis to HSCT (<140 days) (71% vs. 36%, p=0.02). In multivariate analysis (Table II), 3-year OS was greater in patients who did not receive pre-HSCT chemotherapy (RR of death 0.29, 95% CI 0.04–0.78, p=0.02) and in those who received HSCT after 1999 (RR 0.17, 95% CI 0.04–0.78; p=0.02). MDS group, cytogenetics, IPSS risk, time from diagnosis to transplant, pre-HSCT BM blast percentage and donor source had no impact on 3-year OS in multivariate analysis.

Disease Free Survival

DFS was 62% (95% CI 44–75%) and 48% (95% CI 31–63%) at 1 and 3-years. At 10 years DFS is similar at 45% (95% CI 28–60%) (Figure 1B) In univariate analysis, improved DFS at 3-years was found for patients who did not receive pre-HSCT chemotherapy (60% vs. 0%, p<0.01) (Figure 2A), those who had a pre-HSCT BM blast percentage <5% (59% vs. 20%, p=0.04) and those who had a time from diagnosis to HSCT of <140 days (71% vs. 26%, p<0.01) (Figure 2B). Decreased DFS was observed in recipients of MMURD marrow (17% vs. 65% in UCB, 53% in MRD and 43% in MURD, p=0.03). In multivariate analysis (Table II) improved DFS at 3-years was associated with not receiving pre-HSCT chemotherapy (RR 0.30, 95% CI 0.10–0.88; p=0.03) and a shorter interval (<140 days) from time of diagnosis to HSCT (RR 0.27, 95% CI 0.09–0.80; p=0.02). Patients with an IPSS risk of Int-2 had a trend toward lower DFS although this was not quite statistically significant (RR 2.97, 95% CI 0.95–9.33; p=0.06). Cytogenetics, pre-HSCT BM blast percentage and

donor source had no significant impact on 3-year DFS in multivariate analysis. Because pre-HSCT chemotherapy and interval from diagnosis to transplant were clearly associated with outcome, we also analyzed this group separately. There were 16 patients who did not receive pre-HSCT chemotherapy and were transplanted <140 days from diagnosis. Donor sources for this group included 5 UCB, 3 MURD and 8 MRD. Three year OS and DFS were both 80% (95% CI 51–93%) (Figure 2C).

Relapse

The incidence of relapse at 2-years was 20% (95% CI 7–33%). Factors associated with decreased risk of relapse at 2-years in multivariate analysis were secondary MDS (RR 0.12, 95% CI 0.02–0.86; $p=0.03$) and not receiving pre-HSCT chemotherapy (RR 0.13, 95% CI 0.03–0.52; $p<0.01$). A shorter time from diagnosis of MDS to HSCT was associated with lower relapse in univariate analysis (11% vs. 28%, $p=0.05$), but this association did not hold true in multivariate analysis. Pre-HSCT BM blast percentage did not significantly affect relapse rates in either the univariate analysis or multivariate analysis. Additionally, the presence of aGVHD and cGVHD was not correlated with relapse.

Treatment Related Mortality and GVHD

Treatment-related mortality was 25% (95% CI 11–39%) at 2-years. In multivariate analysis, the risk of TRM was increased in those who had a time from diagnosis to HSCT of ≥ 140 days (RR 9.86, 95% CI 1.28–76.22; $p=0.03$). MDS group, IPSS risk, pre-HSCT blast percentage, pre-HSCT chemotherapy, transplant year and donor source had no significant impact on TRM. The incidence of grade II–IV and III–IV aGVHD at 100 days was 41% (95% CI 24–57%) and 16% (95% CI 5–28%), respectively, while the 1-year incidence of cGVHD was 19% (95% CI 6–32%).

DISCUSSION

In this single center study, we show that pediatric patients with MDS who received myeloablative HSCT early after the diagnosis and without pre-HSCT chemotherapy showed significantly improved outcomes (3 year OS and DFS of 80%) relative to those transplanted >140 days from diagnosis and/or after induction chemotherapy. The combination of these two variables and their association with improved outcomes is novel and has not been previously reported. While they need to be validated, these results suggest that proceeding to HSCT early in the disease is indicated.

Survival rates in this series are similar to previously published results [12,15]. Our patients had an estimated OS of 53% and DFS of 48% at 3-years. Remarkably, these survival rates are essentially unchanged at 10 years post HSCT. Published data are limited, as many studies define MDS with different parameters, with some including the diagnoses CMML, JMML, and MDS-AML. Among studies limiting MDS to include RA/RARS (refractory anemia with ringed sideroblasts), RAEB, and RAEB-T according to the FAB or modified WHO classification, estimates of disease- or event-free survival range anywhere from 38 to 60.9% at 10 months to 8 years [8,12–14,16]. In our study, OS, DFS, and engraftment results improved after 1999. Advances in supportive care and HLA-typing likely are major contributors to this improvement, as has been previously demonstrated in adults [29]. Woodard et al., in their evaluation of unrelated HSCT for MDS, also reported decreased cGVHD after 1994, which the authors attribute to improved HLA-matching [12]. Rocha et al. similarly reported year of transplant as a predictive factor, but cite decreased TRM after 2001 as the reason [13].

In our study, TRM was the greatest contributor to mortality at 25%. Several other pediatric studies report similar TRM rates, with a range of 21–59% [9,12,14,15,17,30]. Because of this, reduced intensity conditioning (RIC) HSCT has been investigated and shown to be well tolerated among adults with hematologic malignancies [31]. Although these studies show decreased TRM, they report higher relapse rates, leading to an overall similar DFS [32–34]. RIC HSCT outcomes in children are more limited, as this conditioning approach is less prevalent in pediatrics. Strahm et al., in a prospective pilot study of the European Working Group for MDS, reported an EFS of 74% after RIC HSCT, which is similar to survival rates following standard myeloablative conditioning with HLA-identical donors [9,35]. Andolina et al., however, reported a lower relapse free survival amongst children receiving RIC HSCT for MDS (47%) [36]. Further pediatric prospective studies will be necessary to delineate whether RIC can effectively reduce TRM while improving overall survival rates in MDS.

We identified improved DFS in patients who had a shorter time from diagnosis to HSCT (defined as <140 days). These results are consistent with those published by Rocha et al. where among pediatric patients receiving unrelated UCB transplant <6 months after diagnosis, there was a 66% 3-year probability of DFS, compared to 20% if HSCT was delayed [13]. Strahm et al. reported mixed results for early transplant (<4 months from diagnosis to HSCT) in advanced MDS, citing reduced TRM, but increased relapse [15]. In contrast, our analysis identified no correlation between the time from diagnosis to HSCT and relapse. The exact explanation of why early transplantation might be associated with improved outcomes is not entirely clear, but may be due to less transfusion support and lower rates of allo-sensitization. As the number of studies commenting on the importance in the time from diagnosis to transplant is limited, further comparison is difficult. Our results suggest that early referral for HSCT after diagnosis is preferred when possible.

Patients in our study who did not receive pre-HSCT chemotherapy had better outcomes (improved OS, DFS and relapse rates) than those who received chemotherapy. In adults, pre-HSCT chemotherapy resulting in a complete remission (BM blast count <5%) marrow is associated with lower relapse [37]. In our study, however, a BM blast count <5% did not significantly affect relapse rates nor was it associated with pre-HSCT chemotherapy use. Historically, pediatric patients have been treated similarly to adults with MDS, and children have tolerated intensive chemotherapy prior to HSCT well with limited toxicities [38]. However, pediatric MDS studies report a relatively poor response to chemotherapy prior to HSCT [39,40], and intensive chemotherapy and lower blast counts prior to transplant are not associated with improved relapse rates, survival, or lower TRM [12,15]. As all of our patients received myeloablative conditioning, we cannot comment on blast count or pre-HSCT chemotherapy prior to a RIC HSCT; however, our results would suggest that chemotherapy before myeloablative HSCT for pediatric MDS is associated with worse outcomes.

As with any single institution report, the major limitation to this study is the small sample size which limits the applicability of the results without further confirmation in larger groups of patients. Additionally, given the retrospective nature of the report, the cohort was heterogeneous with regard to diagnostic methods, pre-HSCT chemotherapy, timing of referral and donor source which also limits the strength of the conclusions that can be drawn. However, all patients were treated at a single transplant institution and therefore transplant procedures, HLA typing, supportive care and post transplant care was uniform.

In summary, this study demonstrates the importance of early HSCT without prior chemotherapy in children with MDS. Some caution must be invoked when interpreting our results, however, considering that the approach to MDS has evolved with the FDA approval of DNA methyltransferase inhibitors like 5-azacytidine and decitabine. While this class of

drugs is not curative, they do have the potential to modify the course of MDS, perhaps altering the burden of malignant cells. As well, they have the potential to alter sensitivity to chemotherapy and/or alloreactive (graft-versus-leukemia) responses [41]. Data on the effect of pre-HSCT hypomethylation on post-HSCT outcomes are limited. Retrospective reports in adults show that the treatment is well tolerated and that outcomes are at least similar to historical controls receiving induction chemotherapy or no pre-HSCT therapy [42, 44]. The effect of these agents on pediatric MDS remains unknown, highlighting the need for cooperative group national and/or international trials. We look forward to future studies examining whether use hypomethylating agents, either before or after transplantation, might impact overall outcomes. Future studies focusing on the use of RIC regimens with the goal of reducing TRM and late effects in long term survivors are also needed.

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Figure 1. Kaplan-Meier Analysis of Overall Survival and Disease Free Survival

A. Overall Survival. OS was 70% (95% CI 53–82%) at 1 year and 53% (95% CI 36–68%) at 3 years and beyond. **B. Disease Free Survival and Relapse.** DFS was 62% (95% CI 44–75%) at 1 year and 48% (95% CI 31–63%) at 3 years and 45% (95% CI 28–60%) at 10 years. The incidence of relapse was 20% (95% CI 7–33%) at 2 years and 26% (95% CI 11–41%) at 10 years.

A.

B.

C.

Figure 2.

A. Kaplan-Meier Analysis of 3-year DFS by Pre HSCT Chemotherapy Status. 3-year DFS was 60% (95% CI 40–75%) for patients who did not receive pre HSCT chemotherapy and 0% for patients who received pre HSCT chemotherapy ($p<0.01$). B. Kaplan-Meier Analysis of 3-year DFS by Time from Diagnosis to HSCT. 3-year DFS was 71% (95% CI 44–87%) in patients who had a diagnosis to HSCT time of <140 days and 26% (95% CI 10–47%) in those with diagnosis to HSCT time of ≥ 140 days ($p<0.01$). C. Kaplan-Meier Analysis of 3-year DFS in Patients who did not receive pre HSCT Chemotherapy and who were transplanted <140 days from Diagnosis. 3-year DFS was 80% (95% CI 51–93%) in the 16 patients who did not receive pre HSCT chemotherapy and were transplanted <140 days from diagnosis.

Table I

Patient Characteristics

Characteristic	N (%)
Total patients	37
Gender	
Male	18 (49)
Female	19 (51)
Median age at diagnosis (years)	11 (1–21)
Type of MDS	
Primary	20 (54)
Secondary	17 (46)
Modified WHO MDS Classification (at diagnosis)	
RC	30 (81)
RAEB	7 (19)
IPSS risk	
Low	1 (3)
INT-1	15 (41)
INT-2	21 (57)
Cytogenetics *	
Monosomy 7	21 (57)
Trisomy 8	7 (19)
Normal/ Other **	8 (22)
Pre HSCT chemotherapy	
Yes	7 (19)
No	30 (81)
Time from diagnosis to HSCT (days)	
<140	18 (49)
140	19 (51)
Year of HSCT	
1990–1999	24 (65)
2000–2010	13 (35)
Pre-HSCT Blast count	
<5%	27 (73)
5%	10 (27)
Graft source	
UCB	9 (24)

Characteristic	N (%)
MRD	15 (41)
MURD	7 (19)
MMURD	6 (16)
HLA match	
Match	20 (54)
Mismatch	17 (46)
CsA containing GVHD prophylaxis	
Yes	29 (78)
No	8 (22)

MDS= Myelodysplastic Syndrome. Primary MDS= de novo. Secondary MDS= 4 treatment-related, 8 with preceding idiopathic aplastic anemia, 3 with Schwachman Diamond syndrome, and 2 familial. WHO= World Health Organization. RC= refractory cytopenia, RAEB= refractory anemia with excess blasts. IPSS= international prognostic scoring system. INT-1= intermediate 1. INT-2= intermediate 2. HSCT= hematopoietic stem cell transplant. UCB= umbilical cord blood, MRD= matched related donor, MURD= matched unrelated donor, MMURD= mismatched unrelated donor. CsA= cyclosporine A. GVHD= Graft versus host disease.

* Cytogenetics not available for 1 patient.

** Other chromosome abnormalities included: chromosome 3 abnormalities (n=1), isochromosome 7q (n=2), 11q23 abnormality (n=1), loss of 5q and 7q (n=1).

Table II

Multivariate Analysis of Overall Survival and Disease-Free Survival.

		Hazard Ratio	95% CI	P-value
3 Year Overall Survival				
Type of MDS	Primary	1.0		0.23
	Secondary	1.95	(0.65–5.83)	
Year of HSCT	<2000	1.0		0.02
	2000	0.17	(0.04–0.78)	
Pre-HSCT therapy	Yes	1.0		0.02
	No	0.29	(0.10–0.84)	
Gender	Male	1.0		0.10
	Female	2.49	(0.83–7.49)	
3 Year Disease-Free Survival				
Type of MDS	Primary	1.0		0.33
	Secondary	0.59	(0.21–1.71)	
Year of HSCT	<2000	1.0		0.07
	2000	0.3	(0.08–1.09)	
Pre-HSCT therapy	Yes	1.0		0.03
	No	0.3	(0.10–0.88)	
IPSS	Int-1	1.0		0.06
	Int-2	2.97	(0.95–9.33)	
Time from Diagnosis to HSCT	140 days	1.0		0.02
	<140 days	0.27	(0.09–0.80)	

IPSS= International prognostic score. MDS= Myelodysplastic syndrome. UCB= Umbilical cord blood, MRD= matched related donor, MURD= matched unrelated donor, MMURD= mismatched unrelated donor.