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Outcomes after Umbilical Cord Blood Transplantation for Myelodysplastic Syndromes

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Abstract

For patients with hematologic malignancies undergoing allogeneic hematopoietic cell transplantation, umbilical cord blood transplantation (UCBT) has become an acceptable alternative donor source in the absence of a matched sibling or unrelated donor. However, there have been few published series dedicated solely to describing the outcomes of adult patients with myelodysplastic syndrome (MDS) who have undergone UCBT.

From 2004 to 2013, 176 adult MDS patients underwent UCBT as reported to the Center for International Blood and Marrow Transplant Research. Median age at the time of transplant was 56 years (range 18–73 years), with 10% having very low, 23% low, 19% intermediate, 19% high, and 13% very high-risk Revised International Prognostic Scoring System (IPSS-R) scores, respectively. The 100-day probability of Grade 2–4 acute graft-versus-host disease (GVHD) was 38%, and the 3-year probability of chronic GVHD was 28%. The probability of relapse and transplant-related mortality (TRM) at 3 years was 32% and 40%, respectively, leading to a 3-year, disease-free survival (DFS) of 28%, and overall survival (OS) of 31%. In multivariate analysis increasing IPSS-R score at time of HCT was associated with inferior TRM ($P=.0056$), DFS ($P=.018$), and OS ($P=.0082$), but not with GVHD or relapse. Pre-transplant comorbidities were associated with TRM ($P=.001$), DFS ($P=.02$), and OS ($P=.001$). Reduced conditioning intensity was associated with increased risk of relapse (RR 3.95; 95% CI 1.78–8.75, $P<.001$), and although

a higher proportion of myeloablative UCBTs were done for those with high-risk disease, the effect of conditioning regimen intensity was the same regardless of IPSS-R score.

For those who lack a matched sibling or unrelated donor, UCBT can result in long-term, disease-free survival for some patients. However, the success of UCBT in this population is hampered by a high rate of TRM.

Keywords

umbilical cord transplantation; blood and marrow transplantation; myelodysplastic syndrome

Introduction

Widespread application of innovative sequencing technologies is rapidly unraveling the biologic underpinnings driving the pathogenesis of the myelodysplastic syndromes (MDS). Nonetheless, allogeneic hematopoietic cell transplantation (HCT) remains the only therapeutic modality that has demonstrated curative potential, with patients surviving in unmaintained remission for more than two decades after HCT [1]. However, only one-in-four patients will have a sibling donor that is matched for human leukocyte antigens (HLA), which is likely to decline as the average family size in the United States declines [2]. Moreover, older MDS patients are likely to have older siblings, increasing the chance of potential donors being found to be unsuitable due to comorbid conditions. With the development of robust donor registries, an HLA-matched donor can be identified for approximately 75% of Caucasian recipients, with successful matching being much more limited for other ethnic groups [3, 4]. Therefore, alternative donor sources have been actively explored. Umbilical cord blood (UCB) is an alternative hematopoietic cell source with two distinct advantages. One being a relative tolerance of HLA disparity, and the other, as a cryopreserved stem cell source, a rapid availability with flexible timing of transplant [5, 6]. A major drawback of UCB as a donor source is the limited number of cells leading to a delayed time to engraftment and immune reconstitution. This has been overcome, in part, by the use of two cord blood units, or ex vivo expansion of a cord blood unit prior to infusion [7, 8]. Over the past decade, improved cord blood unit selection, conditioning, and supportive care have all led to improved outcomes in adults after UCB transplant (UCBT). Contemporary retrospective analyses suggest that disease-free survival after UCBT for hematologic malignancies is comparable to that of matched-related or unrelated donors [9–11].

Many of the large studies evaluating UCBT have included patients with MDS, however their post-transplant outcomes can only be described through subgroup analyses. There have been few published series solely describing the outcomes of adult patients who have undergone UCBT for MDS [12–14]. In the absence of substantial data, patients that could benefit from UCBT may not be offered the treatment option when they otherwise would be considered for matched related or unrelated donors. Likewise, clinical trials in HCT also may exclude cord blood as a donor source, such as Blood and Marrow Clinical Trials Network (BMT-CTN) 1102 [15]. Treatment decisions and clinical trial design can be aided by providing a description of UCBT for MDS that incorporates a large number of patients from multiple

centers. Therefore, we conducted a descriptive analysis of patients who have undergone UCBT for MDS as reported to the Center for International Blood and Marrow Transplantation Research (CIBMTR). We also sought to validate the ability of MDS disease-risk models to predict post-HCT outcomes.

Patients and Methods

Data Sources

The CIBMTR is a combined research program of the Medical College of Wisconsin and the National Marrow Donor Program, which consists of a voluntary network of more than 450 transplantation centers worldwide that contribute detailed data on consecutive allogeneic and autologous transplants to a centralized statistical center. Observational studies conducted by CIBMTR are performed in compliance with all applicable Federal regulations pertaining to the protection of human research participants. Protected health information issued in the performance of such research is collected and maintained in CIBMTR's capacity as a Public Health Authority under the Health Insurance Portability and Accountability Act Privacy Rule. Additional details regarding the data source are described elsewhere [16].

Patients

Adult patients (age ≥ 18 years) with MDS who underwent their first transplant between 2004 and 2013 were included (N=2709). Patients with HLA-matched sibling, matched or mismatched unrelated donor (URD), haploidentical or syngeneic donor, and those missing donor data, were excluded from this analysis (N=2518). An additional 15 patients were excluded due to missing 100-day follow-up data.

Cytogenetics were classified based on those identified by the MDS Comprehensive Cytogenetic Scoring System [17]. Monosomal karyotype was defined as persons that have monosomy of two or more chromosomes or one single autosomal monosomy in the presence of other structural abnormalities [18]. Overall disease risk at the time of transplant was stratified by the Revised International Prognostic Scoring System (IPSS-R) [19].

Study Endpoints

Primary endpoints included transplant-related mortality (TRM), relapse, overall (OS), and disease-free survival (DFS). TRM was defined as death from any cause in the first 28 days post-transplantation irrespective of relapse status. Death beyond day +28 was considered to be transplant-related if the disease state was remission. DFS was defined as time to relapse or death from any cause. OS was defined as time from transplantation to death from any cause. Patients were censored at last follow-up.

Secondary endpoints included hematopoietic recovery, as well as the incidence of acute and chronic graft-versus-host disease (GVHD). Neutrophil and platelet engraftment were defined as the time from transplantation to a neutrophil count (ANC) $>0.5 \times 10^9/L$ (first of 3 consecutive days), and time to platelets $\geq 20 \times 10^9/L$ (first of 3 consecutive days and no platelet transfusions 7 days prior), respectively. GVHD, both acute and chronic, were graded

per consensus criteria [20, 21]. Conditioning regimen intensity was determined according to the CIBMTR Reduced-Intensity Conditioning (RIC) Regimen Workshop [22].

Statistical Analysis

Descriptive tables of patient, disease, and transplant-related variables for patients receiving UCBT for MDS were generated. Univariate probabilities of OS and DFS were calculated using the Kaplan-Meier estimator; the log-rank test was used for univariate comparisons. Probabilities of graft failure, acute and chronic GVHD, TRM, and relapse were calculated using cumulative incidence functions to accommodate competing risks.

Assessment of potential risk factors for post-HCT outcome was evaluated in multivariate analyses using the Cox proportional hazards model that included age and Karnofsky performance status at time of transplantation, comorbidity score (HCT-CI), recipient CMV status, MDS risk score, primary versus secondary MDS, single versus double cord blood units transplanted, nucleated cell dose, year of transplantation, conditioning regimen intensity, use of serotherapy (anti-thymocyte globulin or alemtuzumab) in the condition regimen, and type of GVHD prophylaxis (tacrolimus-based versus cyclosporine-based versus other) as covariates. Two models were built: 1) with IPSS-R as the main effect; and 2) with the proposed CIBMTR MDS Transplantation Risk Score [23] as the main effect. The latter model was developed and validated among MDS patients (training $n = 1,151$; validation $n = 577$) who underwent allogeneic HCT from either an identical sibling donor or a well-matched unrelated donor. The two risk scores were compared using concordance probability [24]. To account for center effect, the marginal Cox model was performed [25]. Backward elimination procedure, with a p -value $<.05$, was used to select significant covariates. Interactions between the main effect and significant covariates were examined.

Results

Patient, Disease, and Transplantation Characteristics

Patient and disease characteristics are presented in Table 1. We identified 176 adult MDS patients, including 21 with CMML, who underwent UCBT, at 59 centers, between 2004 and 2013. The median number of transplants per center was 2 (range 1–26). With 34% being over the age of 60 years, the median age at the time of transplantation was 56 years (range 18–73). Most patients had Karnofsky Performance Scores (KPS) of 90–100%, and 32%, 27%, 34% of patients had HCT-CI scores of 0, 1–2, or 3, respectively.

The median time from diagnosis to UCBT was 9 months (range 1–147). Cytogenetic data and IPSS-R scores at the time of transplant were available for 92% and 84% of patients, respectively. A majority of patients (77%) received some form of cytoreductive therapy, predominantly hypomethylating agents, prior to transplantation, and 72% had 5% blasts or less on their pre-HCT bone marrow biopsy.

Myeloablative conditioning regimens were given to 61 (35%), and 77 (30% of myeloablative, 51% of RIC/non-myeloablative) patients received either anti-thymocyte globulin or alemtuzumab as part of their conditioning. Double cord blood units were used in 80% of transplants, with median total nucleated cell dose (TNC) of $4 \times 10^7/\text{kg}$ (range <1 –29

$\times 10^7/\text{kg}$). As expected, conditioning regimen intensity was associated with age at the time of transplantation ($P=.001$), but was not associated with receiving a single or double cord blood unit ($P=.58$).

Considering the unit with the higher number of human leukocyte antigen (HLA) incompatibilities with the recipient, 60% of recipients had 2 or more mismatches. GVHD prophylaxis regimens were primarily based on a combination calcineurin inhibitor (tacrolimus or cyclosporine) with mycophenolate mofetil (80%). The median follow-up of survivors was 37 months (range 3–78 months). The completeness of follow up was 98%, 93%, and 89% at 1, 2, and 3 years, respectively [26].

Hematopoietic Recovery

The cumulative incidence of neutrophil recovery at 28 and 100 days after UCBT was 92% (95% CI 88–95%) and 97% (95% CI 95–99%), respectively. The corresponding values for platelet recovery at 28 and 100 days was 66% (95% CI 59–72%) and 86% (95% CI 81–90%), respectively.

GVHD, Relapse, Treatment-Related Mortality, and Survival Outcomes

The cumulative incidence acute GVHD at day 100 was 38% (95% CI 30–45%) and 14% (95% CI 9–20%), for Grades 2–4 and 3–4, respectively (Table 2). The probability of chronic GVHD at 1 year was 26% (95% CI 19–33%), and 28% (95% CI 21–36%) at 3 years.

The probability of relapse at 3 years was 32% (95% CI 25–40%), with the latest relapse occurring at 22 months after UCBT (Table 2, Figure 1).

The 3-year probabilities of TRM, DFS, and OS were 40% (95% CI 33–48%), 28% (95% CI 21–35%), and 31% (95% CI 24–39%), respectively (Table 2, Figure 1). The most common cause of death was persistence or relapse of MDS (45%), followed by infection (16%) and organ failure (13%). Graft failure accounted for only 3% of deaths (Table 3)

Impact of IPSS-R at the time of UCBT

In multivariate analysis using marginal Cox model to adjust for center effect, IPSS-R at the time of HCT was associated with TRM ($P=.006$), DFS ($P=.02$), and OS ($P=.008$, Table 4, Figure 2). IPSS-R was not associated with the incidence of acute ($P=.52$) or chronic GVHD ($P=.66$), as well as disease relapse ($P=.86$). RIC/non-meyloablative (NMA) conditioning regimens were associated with an increased risk of relapse relative to myeloablative regimens (HR 3.95, 95% CI 1.78–8.75; $P=.0007$, Supplemental Figure 2), and a higher proportion of myeloablative HCTs were done for those with high-risk disease by IPSS-R. However, the interaction between conditioning intensity and IPSS-R for relapse ($P=.17$) and TRM ($P=.033$) were not significant. In this model, HCT-CI was also associated with TRM ($P=.001$), DFS ($P=.02$), and OS ($P=.001$, Table 4, Supplemental Figure 1).

Validation of CIBMTR MDS Transplantation Risk Score

In multivariate analysis using marginal Cox model to adjust for center effect, the CIBMTR MDS risk score was not associated with any of the outcomes (Table 5, Figure 3). As with the

previous model, where IPSS-R was the main effect, RIC/NMA conditioning regimens, relative to myeloablative regimens, were associated with relapse ($P=.0008$). Also, HCT-CI was associated with TRM ($P=.02$), DFS ($P=.03$), and OS ($P=.001$) as seen when IPSS-R is the main effect.

Discussion

The extensive adoption of disease-modifying drugs, such as the hypomethylating agents and lenalidomide, along with better supportive care, have contributed to better outcomes for patients with MDS over time. In the same fashion, outcomes for patients undergoing allogeneic hematopoietic cell transplantation have improved [27], which can also contribute a positive effect, and potential of cure, for patients with MDS. However, in a disease common to an older population, suitable sibling donors may not be available. In the absence of matched unrelated donors, alternative donor sources are often considered. In the current study, we described the outcomes of 176 patients who underwent UBCT for MDS as reported to the CIBMTR. We found that the 3-year probabilities of chronic GVHD, relapse, TRM, DFS, and OS were 28%, 32%, 40%, 28%, and 31%, respectively.

In the current study, the median age was 56 years, which indicates an older cohort as compared to other published studies. For example, in the report by Sato and colleagues, the median age at the time of transplantation was 42 years [12]. Other key differences in baseline characteristics between this study and ours, make a direct comparison of the results difficult. For example, all of the patients in the current study had MDS, excluding those who progressed to AML, whereas in the study by Sato et al, 79% of patients had transformed to AML.

Although a formal statistical analysis was not performed, we found that post-HCT survival in this cohort was substantially lower than what has been described in a contemporary cohort that included matched related and unrelated donors also conducted by the CIBMTR [23]. There is a stark difference between the 3-year DFS of 28% (95% CI 21–35%) in this study, compared to matched unrelated donors in the contemporary study (41%, 95% CI 38–44% for the training cohort; 44%, 95% CI 40–48% for the validation cohort). This difference is a product of a relative increase in the incidence of TRM, and to a lesser extent, relapse.

The European Group for Blood and Marrow Transplantation (EBMT) reviewed a group of 129 patients with MDS that underwent UCBT, finding similar results with 2-year probabilities of chronic GVHD, relapse, TRM, DFS, and OS of 23%, 30%, 42%, 28%, and 30%, respectively [14]. One key difference between the two studies, is that a majority (71%) of the patients in the EBMT analysis had progressed to acute myeloid leukemia prior to transplantation, with less than half (48%) of them in remission prior to transplantation. In the current study, only 28% has a blast count over 5% at the time of transplantation. In the EBMT study, the investigators also went on to compare the outcomes of MDS patients who underwent UCBT with 502 contemporary patients who had matched related or unrelated donors using peripheral blood (PB) as a hematopoietic progenitor cell source. As compared to UCBT, those who underwent PB transplantation had similar rates of GVHD and relapse,

but a better 2-year TRM (31% vs. 42%, $P=.03$), DFS (44% vs. 28%, $P<.0001$), and OS (49% vs. 30%, $P<.0001$).

Another report from Japan Society for Hematopoietic Cell Transplantation Data Registry, described the outcomes of 431 patients that underwent UCBT and compared to a contemporary cohort of 1093 patients that underwent unrelated donor transplant [13]. They found that the estimated 5-year OS was inferior for UCBT as compared to unrelated donors (32% vs. 46%, $P<.0001$). UCBT and unrelated donor transplant had similar rates of TRM (3-year cumulative incidence of TRM was 34% vs. 36%), however UCBT had a higher incidence of relapse (20% vs. 10%, $P<.001$).

In contrast to other reports, the current study is unique in that it validated predictive models for post-HCT outcomes. Interestingly, IPSS-R, a model that specifically quantifies disease risk, calculated at the time of HCT did not predict for post-HCT relapse, but did for TRM. While it is clear that disease burden before transplantation is a predictor of relapse [28, 29], the optimal pre-HCT therapy has yet to be defined [30, 31]. Approximately three quarters of the patients received some form of pre-HCT cytoreductive therapy. There was no association between pre-HCT therapy and post-HCT outcome. Although, relapse was the most common cause of death for patients with lower and intermediate-risk disease, mortality from transplant-related complications was increased in those with higher-risk disease (Table 3). Those with higher IPSS-R may have received pre-HCT therapies of greater duration and intensity, and cumulative toxicity may explain the association between disease-risk and TRM. However, the number or types of pre-HCT therapy did not vary with the pre-transplant IPSS-R risk-groups. Another limitation of this analysis is the fact that the pre-HCT IPSS-R score was missing in 16% of patients.

The CIBMTR MDS Transplantation Risk Score, a model specifically developed to predict post-HCT outcomes in patients with MDS [23], was not found to be predictive in this analysis. While the donor sources were different, the current study's cohort had a similar median age, performance status, pre-transplant blast count, and cytogenetic risk to the cohort used to build the MDS transplant risk model. However, in the current study, a higher proportion of patients received pre-transplant cytoreductive therapy, and there were noteworthy differences in the conditioning regimens that patients received. In the current study, more patients received either antithymocyte globulin or alemtuzumab as part of conditioning, and a larger proportion of patients in the MDS transplant risk model derivation cohort underwent myeloablative conditioning. It is important to note that the CIBMTR MDS Transplantation Risk Score was missing for 35 (20%) patients, therefore limiting the statistical power to determine the utility of the model in this population.

The median time from diagnosis to UCBT in the current study is comparable to previous reports [12, 14]. In patients with limited donor options, increased effort is put in to the search process and evaluation of alternative donor sources. This can add time to the pre-transplant period resulting in a lead-time bias. This bias could positively influence post-HCT outcomes, as patients with more aggressive disease may not have enough time to secure a donor and undergo HCT, therefore are not included in the subsequent analysis. Conversely, lead-time bias could be deleterious to aggregate outcomes as a result of transplanting

patients later in their disease course. Nonetheless, time from diagnosis to HCT for MDS is not associated with outcome in the matched-related or matched-unrelated donor setting [23], as well as the UCBT setting [14].

While the existing data suggest that outcomes with matched related and unrelated transplantation are superior, UCBT does offer long-term disease-free survival for some patients. With relapse being the primary contributor to mortality after transplantation, strategies to reduce relapse are needed to improve outcomes irrespective of donor source [32]. This is particularly important for UCBT, as the option of graft manipulation with donor cellular infusion is not available. When comparing donor source, the rates of relapse are similar between different donor sources, where TRM from delayed immunologic recovery stands out as a heightened barrier to success specific to UCBT. Therefore, several manipulation and expansion strategies, with the aim of increasing the cell dose and modifying the composition of cord blood units, are being developed [33, 34]. With increased focus on health care costs and delivering value-based care, the cost of cord blood unit acquisition compared to obtaining a graft from other donor sources presents another potential barrier to wide-spread adoption of UCBT.

As UCBT continues its development, it will do so in parallel with other alternative donor sources including mismatched unrelated and haploidentical donor sources. Use of single mismatch donors significantly increases the available donor pool [4]. However, use of these donors leads to rates of GVHD and TRM that are much higher than expected for fully-matched donor HCT. Multiple strategies have been sought to identify “permissible mismatches” associated with improved outcomes of a single-allele mismatched unrelated donor HCT [35]. Haploidentical transplantation, facilitated by the administration of cyclophosphamide after cellular infusion, has the advantages of following a logistical pattern similar to matched sibling transplantation, and a time to engraftment on par with matched related and unrelated donor transplants [36]. However, data on long-term outcomes is lacking, and like UCBT, the published reports include MDS as a disease subset, not as a primary focus. In order to answer these questions, there is clear need for a prospective study randomizing patients with MDS between haploidentical transplantation and UCBT similar to the ongoing BMT-CTN 1101 study (ClinicalTrials.gov Identifier: NCT01597778). By focusing on the outcomes when different transplantation strategies are applied to individual patient populations, treatment decisions and clinical trial design can better informed. These are moving targets, and as both traditional and alternative donor transplants are refined, they will need continuous evaluation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Use of umbilical cord blood transplant (UCBT) for MDS is not well-described
- Relapse and overall survival at 3 years was 32 and 31%, respectively
- Transplant-related mortality (TRM) at 3 years was 40%
- Disease risk, comorbidities, and conditioning intensity predict outcomes
- UCBT can offer long-term success for some, but is hampered by a high rate of TRM

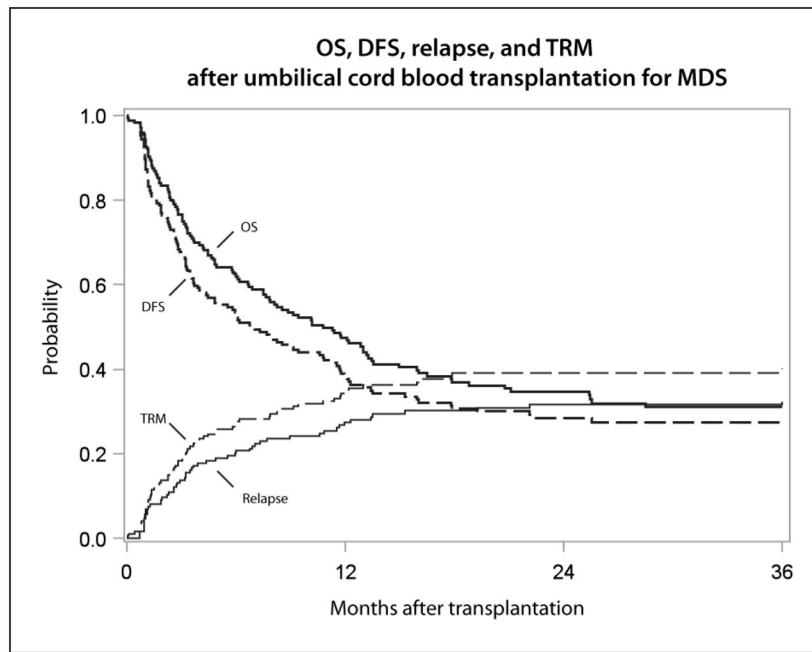


Figure 1. Overall survival, disease free survival, relapse, and transplant-related mortality after umbilical cord blood transplantation for MDS

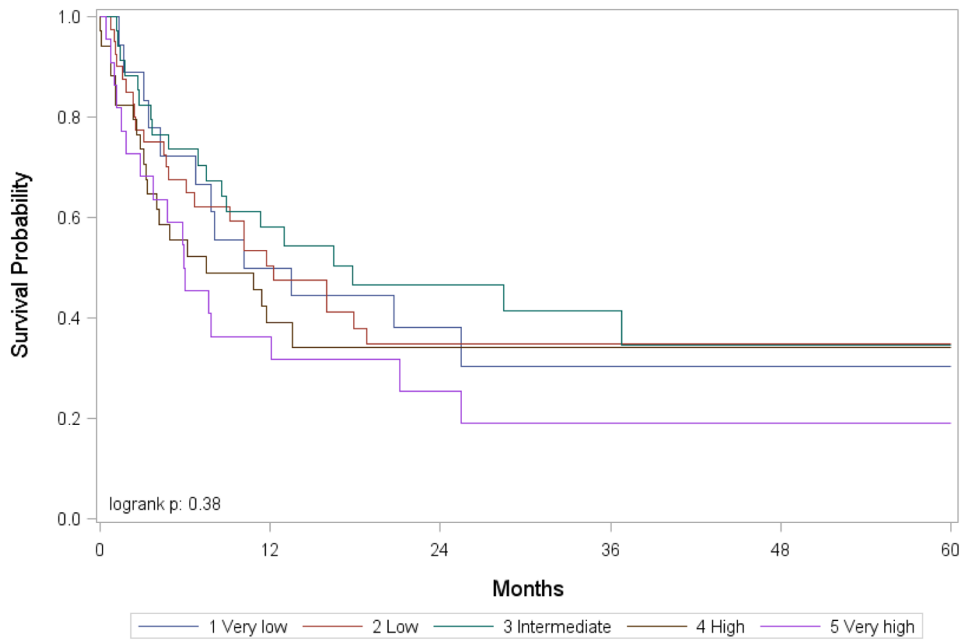


Figure 2. Overall survival after umbilical cord blood transplantation for MDS by pre-transplantation IPSS-R score

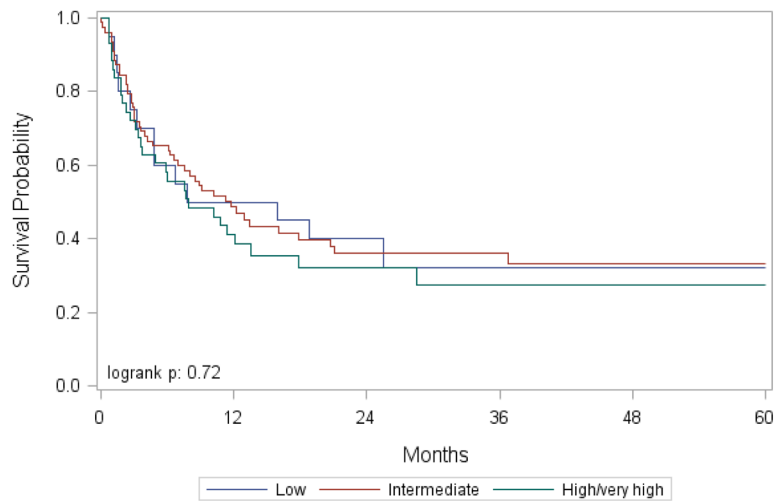


Figure 3.
Overall survival after umbilical cord blood transplantation for MDS by CIBMTR MDS Transplantation Risk Score

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Table 1

Characteristics of patients received allogeneic umbilical cord blood transplantation for MDS between 2004 and 2013

Variable	N (%)
Number of patients	176
<i>Patient-related</i>	
Age, median (range)	56 (18–73)
Gender	
Male	99 (56)
Female	77 (44)
Karnofsky score	
90–100%	127 (72)
< 90%	47 (27)
Missing	2 (1)
Comorbidity score (HCT-CI)	
0	57 (32)
1–2	48 (27)
3	60 (34)
Not available before 2007	11 (6)
Recipient CMV status	
Negative	58 (33)
Positive	117 (66)
Not tested	1 (<1)
<i>Disease-related</i>	
Secondary MDS	
No	146 (83)
Yes	25 (14)
Missing	5 (3)
Pre-transplantation cytoreductive therapy	
Hypomethylating agent only	87 (49)
Intensive chemotherapy only	19 (11)
Hypomethylating agent & intensive chemotherapy	24 (14)
None	40 (23)
Missing	6 (3)
Bone marrow myeloblasts prior to transplantation	
< 5%	127 (73)
5–10%	23 (13)
> 10%	13 (7)
Missing	13 (7)
Blast in blood prior to transplant	

Variable	N (%)
3%	121 (69)
> 3%	12 (7)
Missing	43 (24)
Platelet count prior to transplant	
50 × 10 ⁹ /L	68 (39)
> 50 × 10 ⁹ /L	108 (61)
Cytogenetic risk prior to conditioning	
Good	61 (35)
Intermediate	34 (19)
Poor	34 (19)
Very poor	3 (2)
Monosomal Karyotype	30 (17)
Not tested	2 (1)
Missing/unable to classify	12 (7)
IPSS-R prior to transplant	
Very low	18 (10)
Low	41 (23)
Intermediate	33 (19)
High	34 (19)
Very high	22 (13)
Missing	28 (16)
CIBMTR MDS transplantation risk score [23]	
Low	20 (11)
Intermediate	78 (44)
High	42 (24)
Very high	1 (<1)
Missing	35 (20)
Time between diagnosis and transplant	
0–3 months	54 (31)
3–6 months	56 (32)
6 months	66 (38)
<i>Transplant-related</i>	
Number of cord blood units	
Single cord	36 (20)
Double cord	140 (80)
Cord blood HLA matching	
3/6	4 (2)
4/6	102 (58)
5/6	53 (30)

Variable	N (%)
6/6	4 (2)
Missing	13 (7)
CD34 ⁺ cell dose, median (range), × 10 ⁵ /kg	2 (<1–73)
CD34 ⁺ cell doses	
0–2 × 10 ⁵ /kg	83 (47)
2–4 × 10 ⁵ /kg	51 (29)
4–8 × 10 ⁵ /kg	16 (9)
> 8 × 10 ⁵ /kg	14 (8)
Missing	12 (7)
Nucleated cell doses, median (range), × 10 ⁷ /kg	4 (<1–29)
Nucleated cell doses	
0–2 × 10 ⁷ /kg	13 (7)
2–4 × 10 ⁷ /kg	74 (42)
4–8 × 10 ⁷ /kg	75 (43)
> 8 × 10 ⁷ /kg	5 (3)
Missing	9 (5)
Donor-recipient sex match (1st cord blood unit)	
Male-Male	38 (22)
Male-Female	33 (19)
Female-Male	41 (23)
Female-Female	33 (19)
Missing	31 (18)
Donor-recipient sex match (2nd cord blood unit)	
Male-Male	20 (11)
Male-Female	19 (11)
Female-Male	24 (14)
Female-Female	15 (9)
NA	36 (20)
Missing	62 (35)
Year of transplantation	
2004–2007	24 (14)
2008–2009	62 (35)
2010–2011	46 (26)
2012–2013	44 (25)
Conditioning regimen	
Myeloablative	61 (35)
RIC/NMA	115 (65)
Serotherapy used in conditioning	
ATG alone	76 (43)

Variable	N (%)
alemtuzumab alone	1 (<1)
No ATG or alemtuzumab	99 (56)
GVHD prophylaxis	
Tacrolimus-based	81 (46)
Cyclosporine-based	83 (47)
Other(s)	8 (5)
Missing	4 (2)
Median follow-up of survivors (range), months	37 (3–78)

List of abbreviations: Hematopoietic cell transplantation comorbidity index (HCT-CI), cytomegalovirus (CMV), human leukocyte antigen (HLA), reduced intensity conditioning (RIC), non-myeloablative (NMA), graft-versus-host disease (GVHD)

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Table 2

Univariate analysis results for patients undergoing umbilical cord blood transplantation for MDS between 2004 and 2013

Outcome	Probability of event (95% CI)
Grade 2–4 acute GVHD	
100-day	38 (30–45)%
Grade 3–4 acute GVHD	
100-day	14 (9–20)%
Chronic GVHD	
1-year	26 (19–33)%
3-year	28 (21–36)%
Relapse	
1-year	27 (21–34)%
3-year	32 (25–40)%
Transplant-related mortality	
1-year	34 (27–42)%
3-year	40 (33–48)%
Disease-free survival	
1-year	38 (31–46)%
3-year	28 (21–35)%
Overall survival	
1-year	47 (40–55)%
3-year	31 (24–39)%

Table 3

Cause of death after umbilical cord blood transplantation

Cause of death	IPSS-R Risk Group			Total (%)
	Very low/Low (%)	Intermediate (%)	High/Very high (%)	
Primary disease/Relapse	17 (47)	12 (63)	13 (34)	42 (45)
Infection	7 (19)	3 (16)	5 (13)	15 (16)
Organ failure	4 (11)	0 (0)	8 (21)	12 (13)
GVHD	3 (8)	1 (5)	4 (11)	8 (9)
Idiopathic pneumonitis/ARDS	2 (6)	1 (5)	4 (11)	7 (8)
Other cause	3 (8)	1 (5)	2 (5)	6 (6)
Graft failure	0 (0)	1 (5)	2 (5)	3 (3)

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Multivariate analysis for adult MDS patients who received umbilical cord blood transplantation between 2004 and 2013

Table 4

Relapse															
	N	RR	95% CI Lower Limit	95% CI Upper Limit	95% CI Lower Limit	95% CI Upper Limit	95% CI Lower Limit	95% CI Upper Limit	95% CI Lower Limit	95% CI Upper Limit	95% CI Lower Limit	95% CI Upper Limit	95% CI Lower Limit	95% CI Upper Limit	Overall p-value
IPSS-R															
Very low/Low	64	1													0.8611
Intermediate	34	1.184	0.577	2.429	0.646										
High/Very high	54	1.143	0.576	2.268	0.7017										
Missing	28	1.391	0.65	2.977	0.3955										
Conditioning regimen															
Myeloablative	62	1													0.0007
RIC/NMA	118	3.947	1.781	8.746	0.0007										
TRM															
IPSS-R															
Very low/Low	64	1													0.0056
Intermediate	34	0.682	0.344	1.352	0.2726										
High/Very high	54	1.755	1.12	2.751	0.0141										
Missing	28	2.046	0.926	4.52	0.0766										
HCT-CI															
0	58	1													0.0013
1-2	50	1.178	0.68	2.04	0.5585										
3	61	2.395	1.393	4.118	0.0016										
Missing	11	0.743	0.358	1.539	0.4234										
DFS															
IPSS-R															
Very low/Low	64	1													0.0177
Intermediate	34	0.832	0.504	1.374	0.4728										
High/Very high	54	1.393	1.017	1.906	0.0387										

Relapse					95% CI	95% CI				Overall
Missing	28	1.632	0.946	2.814	0.0782					
HCT-CI										
0	58	1			0.0241					
1-2	50	1.086	0.632	1.867	0.7646					
3	61	1.908	1.164	3.126	0.0104					
Missing	11	1.229	0.715	2.113	0.4551					
OS										
			95% CI	95% CI						
IPSS-R	N	RR	Lower Limit	Upper Limit	p-value					
Very low/Low	65	1			0.0082					
Intermediate	35	0.876	0.51	1.504	0.6303					
High/Very high	55	1.548	1.119	2.142	0.0084					
Missing	28	1.724	0.911	3.262	0.0943					
HCT-CI										
0	60	1			0.0014					
1-2	50	1.108	0.618	1.988	0.7297					
3	61	2.221	1.314	3.755	0.0029					
Missing	12	1.478	0.868	2.517	0.1506					

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Table 5

Multivariate analysis results for patients undergoing umbilical cord blood transplantation for MDS between 2004 and 2013, with the CIBMTR MDS Transplantation Score as the main effect

Relapse				95% CI	95% CI			Overall
	N	RR	Lower Limit	Upper Limit		p-value		p-value
CIBMTR MDS score								
Low	19	1						0.3072
Intermediate	83	0.749	0.281	1.997		0.5631		
High/Very high	44	0.869	0.304	2.486		0.7932		
Missing	34	1.378	0.499	3.805		0.5366		
Conditioning regimen								
Myeloablative	62	1						0.0008
RIC/NMA	118	3.963	1.775	8.85		0.0008		
TRM								
			95% CI	95% CI				Overall
CIBMTR MDS score [23]	N	RR	Lower Limit	Upper Limit		p-value		p-value
Low	19	1						0.7711
Intermediate	83	0.752	0.32	1.768		0.5131		
High/Very high	44	1.044	0.463	2.352		0.9177		
Missing	34	0.802	0.318	2.02		0.6397		
HCT-CI								
0	58	1						0.0225
1-2	50	1.085	0.611	1.928		0.781		
3	61	2.132	1.249	3.638		0.0055		
Missing	11	0.963	0.418	2.22		0.9301		
DFS								
			95% CI	95% CI				Overall
CIBMTR MDS score	N	RR	Lower Limit	Upper Limit		p-value		p-value
Low	19	1						0.3668
Intermediate	83	0.845	0.401	1.782		0.6591		

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Relapse					95% CI	95% CI	Upper Limit	p-value	Overall
High/Very high	44	1.058	0.535	2.092	0.8706				
Missing	34	1.212	0.595	2.468	0.5968				
HCT-CI									
0	58	1			0.0308				
1-2	50	1.093	0.64	1.865	0.7454				
3	61	1.877	1.115	3.161	0.0178				
Missing	11	1.336	0.809	2.206	0.2575				
OS									
CIBMTR MDS score	N	RR	Lower Limit	Upper Limit	p-value				
Low	20	1			0.6573				
Intermediate	85	0.81	0.377	1.738	0.5881				
High/Very high	44	1.062	0.507	2.227	0.8726				
Missing	34	0.939	0.467	1.886	0.8589				
HCT-CI									
0	60	1			0.0016				
1-2	50	1.064	0.591	1.915	0.8364				
3	61	2.084	1.228	3.537	0.0065				
Missing	12	1.738	1.056	2.86	0.0295				