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Stem Cell Transplantation in Pediatric Patients with Myelodysplastic Syndrome at a Single Institution

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Abstract

In MDS, the bone marrow produces abnormal, immature blood cells called blast cells. Imprecise, in half of pediatric MDS, blast count is normal. A retrospective observational study was conducted to review the outcome of our HCT in pediatric patients with MDS. Record of 35 MDS patients after BMT, 1993-2016, were reviewed. Median age at transplant was 4 yrs (0.8-14.8) and median time to transplant from diagnosis 8.1 (2.3-102.5) months. TRM was 17.1% (6); [low risk (LR) = 5 (19.2%) and high risk (HR) = 1 (11.1%)] MDS group succumbed within first 100 days. The rest were fully engrafted; [low risk = 21 (72.4%) and high risk = 8 (27.6%)]. Primary and secondary graft failure was observed in one patient each (2.9%). VOD was seen in 2 patients (5.7%) and 5 (14.3%) had hemorrhagic cystitis. With a median follow-up of 112.4 months and 12 events of mortality, 3-years OS was 68.1% ± 8.0%. No significant risk factor including age, time to transplant, disease risk group, gender, conditioning regimen, source of stem cells, or a GvHD through uni- or multi-variable analyses were found to be associated with OS. Bu/Cy/±ATG conditioning regimen showed a trend of superiority for OS and EFS in our small series. The relapse incidence in our cohort was 11.5% in LR MDS.

Keywords:
myelodysplatic syndromes outcome, children, hematopoietic cell transplantation

Introduction

Myelodysplastic syndromes (MDS) are a heterogeneous group of clonal stem cell disorders, characterized by ineffective hematopoiesis, a variable degree of cytopenia, and an increased risk for developing acute myelogenous leukemia (AML) [1]. MDS with ≥ 2% blasts in PB or ≥ 5% but less than 20% blasts in the BM is classified as MDS-EB in the most recent WHO classification of myeloid neoplasms [2]. The variant MDS-EB in transformation (MDS-EB-t) is retained in the pediatric classification of MDS, [3] and is characterized by a PB or BM blast percentage between 20% and 29%. However, it must be emphasized that the blast percentage in a single specimen is in itself not sufficient for differentiating MDS-EB or MDS-EB-t from AML. MDS is rare in children, presents with advanced disease (MDS-EB and MDS-EB-t) and progress to leukemia more often than adults [4, 5]. Accounting for 4% of all pediatric hematopoietic neoplasia, MDSs are far less common in children than in adults [6]. Majority of the pediatric patients have associated chromosomal abnormalities at presentation, with monosomy 7 being the most frequent [7]. MDS classification that includes some of the FAB subtypes (Juvenile Myelomonocytic Leukemia syndrome and others) has not been universally accepted and today there is a consensus that these disorders are distinct from MDS [8]. An international consensus has been recently achieved on the classification of MDS in childhood. This classification includes refractory cytopenia (RC) and refractory anemia with excess blasts (MDS-EB) [9]. Therapy-related MDS are generally considered separately when given the different etiology, clinical characteristics, and poorer prognosis [10, 11]. There are a number of differences between adult and pediatric manifestation of MDS. In children, refractory anemia (RA) with ringed sideroblasts and MDS associated with del(5q) chromosome are exceedingly rare. In addition, the importance of multilineage dysplasia in RA is unknown. Anemia is generally the main presenting symptom in adults with RA, but in childhood cases, neutropenia and thrombocytopenia are frequently observed. Therefore, “refractory cytopenia” was felt to be a more suitable term for pediatric MDS without excess blasts. Furthermore, in children, there are no data to indicate whether a blast threshold of 20% is better than the traditional 30% to distinguish MDS from de novo AML. To accommodate these characteristics of pediatric MDS, a simple classification scheme based on morphological features and conforming to the WHO suggestions were proposed [1]. It recognizes three diagnostic groups: RC (BM blasts < 5%), RA with excess blasts (RAEB) (BM blasts 5%–20%) and RAEB-T (BM blasts 20%–30%). Allogeneic Hematopoietic Cell Transplantation (HCT) is the treatment of choice for the majority of young patients with MDS or myelodysplastic syndrome-related AML who have a histo-compatible sibling. Disease-free survival ranges from 29% to 40% with a corresponding non-relapse mortality of 37% to 50% and a rate of relapse ranging from 23% to 48%, if the donor is an HLA-identical sibling in patients with advanced disease. If unrelated donors were used, after standard myeloablative conditioning, the treatment-related mortality will exceed 50% [6]. Despite an improvement in the results of allogeneic HCT during the past decade mainly due to a lower treatment-related mortality, there still is a high morbidity, which makes allogeneic stem cell transplantation after standard conditioning only appropriate for younger patients [12]. Graft failure and relapse of the primary disease were the main causes of treatment failure. However, methods to further improve outcome in patients with MDS undergoing allogeneic HCT are needed to decrease the relapse rate. This could be achieved through serial post HCT analysis of chimerism data to

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detect the development of mixed chimerism, which is a predictor of poor outcome, and the use of preemptive immunotherapy with donor lymphocyte infusions or discontinuation of the immunosuppressive therapy. A previous study reporting the results of HCT in MDS from the region has highlighted better outcome in younger patients [13]. We conducted a retrospective observational study to review the outcome of HCT in pediatric patients with MDS treated at King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia.

Patients and methods

A group of 35 transplant naïve pediatric patients (age ≤ 14 years at diagnosis) with MDS who underwent HCT at our institution from Jan 1993 to December 2016 were identified. A total of 37 patients were transplanted in allogeneic fashion from Jan 1993 to December 2016 at our institution. Two (2) were excluded for having previously been transplanted at other hospitals. Data on demographics, diagnosis, transplant-related parameters and outcome were extracted from prospectively maintained clinical databases and through medical charts review. After quality assurance checks, the dataset was then transferred to IBM-SPSS for Windows Version 20.0 for final analyses. Based on WHO Criteria, 26 (74.3%) patients were categorized as Low Risk (LR) and remaining nine (25.7%) as High Risk (HR) MDS. Patients' characteristics and HCT related parameters are presented in table I. All patients received cyclosporine (CsA) or methotrexate (MTX) based graft versus host disease (GvHD) prophylaxis and were conditioned with myeloablative regimen. Conditioning regimens, GvHD prophylaxis, diagnosis and staging of GvHD were based on Center for International Blood and Marrow Transplant Research (CIBMTR) guidelines.

Table I. Patient characteristics, transplant and outcome related parameters

Parameters of interest n (%)	LR 26 (74.3)	HR 9 (25.7)	Total n = 35
Gender			
Female	10 (38.5)	3 (33.3)	13 (37.1)
Male	16 (61.5)	6 (66.7)	22 (62.9)
Age at HCT (years from diagnosis)			
< 5 years	16 (61.5)	5 (55.6)	21 (60)
5–10 years	8 (30.8)	3 (33.3)	11 (31.4)
10 and above	2 (7.7)	1 (11.1)	3 (8.6)
Median (Min-Max)	3.3 (0.8-14.8)	5.0 (3.1-13.6)	4.0 (0.8-14)
Median time to transplant (months from diagnosis)	11.2 (2.3-102.5)	3.7 (2.3-20.1)	8.1 (2.3-102.5)
Monosomy 7 (+)	8 (33.3)	3 (33.3)	11 (33.3)
Source of Stem Cells			
Bone Marrow	23 (88.5)	8 (88.9)	31 (88.6)
Cord Blood	3 (11.5)	1 (11.1)	4 (11.4)
TNC Dose[1] (median) (min-max)	0.5 (0.04-52.5)	0.5 (0.3-58.0)	0.52 (0.4-58.0)
CD34[2] (median) (min-max)	6.2 (0.1-20.3)	6.8 (0.13-12.9)	6.2 (0.1-20.3)
HLA Type			
HLA-Identical Siblings	20 (76.9)	8 (88.9)	28 (80)
HLA-Identical Other Relatives	2 (7.7)	-	2 (5.7)
Related 1-Ag Mismatch	1 (3.8)	-	1 (2.9)
Un-Related 1-AG Mismatch	1 (3.8)	1 (11.1)	2 (5.7)
Un-Related 2-AG Mismatch	2 (7.7)	-	2 (5.7)
Conditioning regimen			
Bu/Cy	9 (34.6)	1 (11.1)	10 (28.6)
Bu/Cy/ATG	7 (26.9)	-	7 (20)
Bu/Cy/VP-16	10 (38.5)	8 (88.9)	18 (51.4)
Donor Gender			
Male	17 (65.4)	7 (77.8)	24 (68.6)
Female	9 (34.6)	2 (22.2)	11 (31.4)
Outcome parameters			
Relapse of the primary disease	3 (11.5)	3 (33.3)	6 (17.1)
Death	8 (30.8)	4 (44.4)	12 (34.4)
Alive – in remission	18 (69.2)	5 (55.6)	23 (65.7)

10^9 per kg; 2. 10^6 per kg

Statistical Considerations

All continuous data are presented as median with minimum and maximum points. For categorical variables, chi-square test for independence was used to test for the independence of association. Kaplan-Meier curves were drawn for survival analysis and tested for any difference between the survival times using the Tarone-Ware test in uni-variate setting. For EFS, primary or secondary graft failure, relapse or death, whichever came first, were considered as event. Cox regression analysis on overall survival data was carried out in multivariable environment to test for the significance of various variables in terms of their role towards survival time.

Results

With a median follow-up time of 112.4±31.7 months, the cumulative probability of five-year overall survival (OS) was 64.5%±8.3% for the whole cohort, 67.1%±9.7% for LR and 55.6%±16.6% for HR MDS patients respectively (p-value: 0.530, Fig. 1). The probability of five-year overall survival same was 72.7%±13.4% in the sub-group of patients with age at transplant between 5-10 years as compared to 66.7%±27.2% in those with over 10 years followed by 60.5%±10.9% who were transplanted in the first five years of their life. However, this difference did not achieve statistical significance (table II). Event Free survival (EFS) for our patients in this study was 64.5%±8.3%.

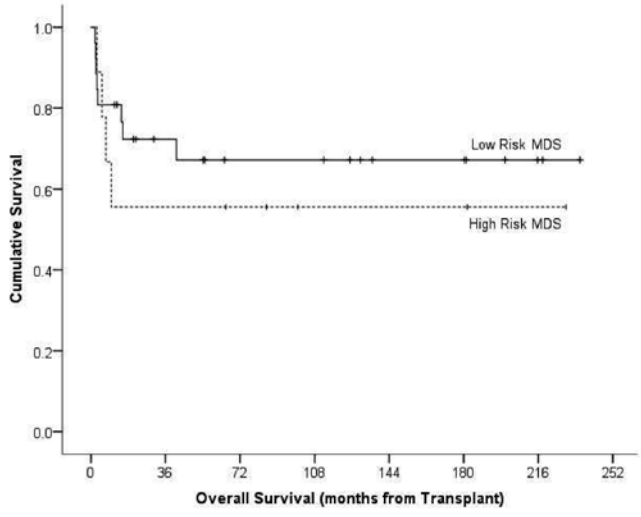

Fig. 1. Overall survival with respect to Risk Groups

Relapse of primary disease was observed in 17.1% (6 of 35; 3 in each of the risk groups). Mortality Rate was significantly lower in non-relapse group 20.7% (6 of 29) compared to the relapsed patients (100%, n = 6; p-value: 0.001) as expected. Five patients who relapsed (83.3%) had received Bu/Cy/VP-16 as conditioning while only one patient (16.7%) from the Bu/Cy/±ATG (ATG-F 10 mg/kg/day x 4 days) conditioning group experienced relapse of the primary disease (p-Value: 0.177).

Based on chimerism studies, 93.9% (31) of evaluable patients (alive) have been engrafted, while among the remaining, one was never engrafted and the other patient, was engrafted and then had a failed graft.

Based on chimerism studies, all those patients alive at Day-100 (n = 29) were fully engrafted; 21 (72.4%) were from LR and eight (27.6%) from HR MDS. Among those at risk (n = 29) beyond Day-100, three patients expired from each risk group as engrafted, thus making our mortality count of twelve at the time of this review.

Cumulative incidence of acute graft versus host disease (aGvHD) was 37.1% (13); ten patients (38.5%) were from LR and three (33.3%) from HR (p-value: 0.749). Overall Grade I aGvHD was seen in seven (53.8%) while Grade II was recorded in six patients (46.2%). No severe Grade III or above aGvHD was observed. There were nine (9) instances of skin a GvHD while seven (7) instances of the same were seen for the gut. No hepatic a GvHD was observed in our group of patients.

The incidence of chronic graft versus host disease (cGvHD) was 21.2% (seven in thirty-three cases at risk; six from LR and one from HR MDS); four (57.1%) had extensive while for the remaining three (42.9%), cGVHD was observed to be limited in grade.

Hemorrhagic cystitis during the same period was seen in five (14.3%) patients (all LR MDS). Veno-occlusive disease (VOD) was seen in two patients (5.7%, all LR MDS) and interstitial pneumonia in one (2.9%, LR MDS) case.

Transplant related mortality (TRM) was 17.1% (6); five (19.2%) patients from LR and one (11.1%) from HR MDS group succumbed within first 100 days of infusion. Of these six patients, two expired engrafted, one had a primary graft failure and the other one post-secondary graft failure (HR MDS) due to progressive disease.

Majority of our patients (28, 80%) had a matched sibling as the donor. When analyzed for survival outcome in this sub-group by conditioning regimens (Bu/Cy/±ATG, n = 13 vs. Bu/Cy/VP-16, n = 15), cumulative probability of five year OS and EFS were better in the former sub-group of patients than the later (83.9±10.4 vs. 53.3±12.9 and 83.9±10.4 vs. 53.3±12.9; p-values: 0.087 and 0.073 respectively). However, the difference did not reach statistical significance. None of the patients who received Bu/Cy/±ATG conditioning experienced relapse of the primary disease compared to those who got Bu/Cy/VP-16 (5 cases, 33%, p-value: 0.044), in the same sub-group, where the donor was a matched sibling.

Relapse of the primary disease was higher in patients with matched sibling donors (5 out of 28, 17.9%) when compared to their counterparts (1 out of 7, 14.3%, p-value: 1.0). The same was lower in LR (3 out of 26, 11.5%) than in HR MDS (3 out of 9, 33.3%, P-Value: 0.162; table I). Both OS and EFS, exhibited better trend in patients for a matched sibling donor (table II). With a median follow-up of 112.4 months and 12 events of mortality (2 within D-100), 3-year overall and event-free survival of our cohort of patients was 0.681±0.080.

In terms of conditioning regimen, non-relapse mortality (n = 5) in LR MDS group was 20% (3 out of 15) in Bu/Cy/±ATG and 25% (2 out of 8) in Bu/Cy/VP-16 regimens respectively (p-value: 1.0). Six patients from those with stable disease at HCT (21.4%) experienced post-HCT relapse of the primary disease compared to none who were in remission (p-value: 0.311). No significant association between the relapse of primary disease and donor HLA-type, age at and

Table II. Cumulative probability of five year survival with respect to factors of interest

	Event Free Survival	P-Value	Overall Survival	P-Value
Age at HCT		0.986		0.990
< 5 years	60.5±10.9		60.5±10.9	
5–10 years	72.7±13.4		72.7±13.4	
≥ 10 years	66.7±27.2		66.7±27.2	
Recipient gender		0.790		0.724
Female	67.3±13.6		67.3±13.6	
Male	62.5±10.6		62.5±10.6	
Monosomy 7 (n = 11)		0.682		0.730
Negative	60.9±11.1		60.9±11.1	
Positive	72.7±13.4		72.7±13.4	
Time to HCT from diagnosis		0.979		0.952
≤ 6 months	63.5±13.1		63.5±13.1	
> 6 months	64.6±11.0		64.6±11.0	
Pre-HCT disease status		0.871		0.927
In remission	71.4±17.1		71.4±17.1	
Not in Remission	63.6±9.2		63.6±9.2	
Conditioning regimen		0.200		0.243
Bu/Cy/±ATG	74.7±11.0		74.7±11.0	
Bu/Cy/VP-16	55.0±11.9		55.0±11.9	
Cell Source		0.547		0.478
Bone marrow	66.7±8.7		66.7±8.7	
Cord blood	50.0±25.0		50.0±25.0	
aGvHD		0.780		0.869
Negative	62.3±10.6		62.3±10.6	
Positive	69.2±12.8		69.2±12.8	
Donor gender		0.427		0.447
Female	50.9±16.3		50.9±16.3	
Male	70.3±9.4		70.3±9.4	
Donor HLA type		0.820		0.763
Matched siblings	67.7±8.9		67.7±8.9	
Others	45.7±22.4		45.7±22.4	

time to transplantation, donor and recipient gender and incidence of a GvHD was found in this study. Among thirty-three patients tested for monosomy 7, eleven (33.3%) were found to be positive. Of these, two patients relapsed (18.2%); one from each risk group and both had a matched sibling donor.

In uni-variate analysis, time to transplant from diagnosis (> 6 months), pre-transplant disease status (In remission vs. Stable disease), donor and recipient gender, monosomy 7 positivity, conditioning regimen (Bu/Cy/±ATG vs. Bu/Cy/VP-16), the source of Stem Cells (Bone marrow vs. Cord blood), or occurrence of aGvHD had no significant impact on EFS and OS time (table II). In multi-variable setting, when adjusted for risk stratification or donor HLA-type, conditioning regimen did not turn out to be of any statistical significance for overall survival (OS).

No secondary malignancy was recorded in our cohort of patients while on follow-up. At the last update, all surviving patients were maintaining sustained donor chimerism.

Discussion

Allogeneic HCT currently offers the best chance of cure and long-term survival for children with advanced MDS [14, 15]. In this article, we reported the outcome of pediatric patients with MDS treated with allogeneic HCT at a single institution. To study a more homogeneous cohort of patients, and in compliance with the recent WHO classification, we excluded patients with secondary MDS (treatment related MDS, and MDS secondary to inborn bone marrow failure syndromes) from this analysis. Myeloablative regimen was used for all of our patients, while for 51.4% it was Bu/Cy /VP-16. The safety profile of etoposide as part of the conditioning regimen has been widely explored in adult studies [16]. In children, however, few studies have addressed the use of high-dose etoposide (40-60 mg/kg) in combination with other agents in the preparative regimens with a lower dose of Bu/Cy. In our study, VP-16 was well tolerated and had less toxicity with no increased incidence of GvHD or VOD. This

finding is comparable with previous study from the same center by Al-Seraihy et al [13]. Late complication of etoposide like secondary malignancy especially AML was not noted in our study. Three-year OS and EFS of our cohort of patients was 0.681±0.080. The probability of five-year overall survival was 0.727±0.134 in the sub-group of patients with age at transplant between 5-10 years as compared to 0.667±0.272 in those with over 10 years followed by 0.605±0.109 who were transplanted in first five years of their life. Historically, HCT with a myeloablative regimen has been reported with an EFS of 75% with TRM being the major cause of treatment failure [17]. In terms of OS and EFS, our results compare favorably with those reported recently by European Working Group of Myelodysplastic Syndromes (MDS) in Childhood (EWOG–MDS) reported the experience with overall, 64 patients are alive after HSCT, an estimate of survival of 63% (53–73) at 5 years with a median observation time of 5.2 years (1.0–10.9), 59 patients are alive in the first complete remission after HSCT. The 5-year probability of EFS after the first allograft is 59% (49–69) [6]. In view of these findings, reduced-intensity conditioning might be an attractive approach at least for patients with hypocellular marrow and normal karyotype [18, 19]. In a pilot study conducted in nineteen children treated at centers affiliated with EWOG-MDS, HCT after a preparative regimen that includes thiotepa and fludarabine resulted in a probability of OS of 84% and an EFS reaching 74% [19]. These results have considerably improved over time, since the last update of the EWOG-MDS reported an OS of 94% and an EFS approaching 88% in 169 patients with RCC [20]. One of the most controversial issues in the treatment of children with advanced MDS is the impact of intensive chemotherapy before HCT. Children with MDS treated on AML protocols have been reported to experience a high rate of induction failure and relapse, resulting in OS of approximately 30% [21-24]. Likewise, patients receiving allogeneic HCT as primary treatment have a considerable risk of relapse, as well as transplantation-related toxicity [21, 25, 26]. Therefore, the role of intensive chemotherapy before HCT for patients with advanced MDS has remained a matter of debate. In this Study, the use of pre-transplant chemotherapy pre-transplant did not seem to improve the EFS or the outcome, although, the small sample size of our study and only 2 patients received chemo may be enabled to conduct comparative analysis. We were unable to do any comparative analysis in this regard as only two patients were treated with pre- transplant chemotherapy in our cohort.

Relapse has been a major contributor to mortality in pediatric patients, with a statistically significant higher relapse rate in MDS- EB and MDS-EB-t cases as compared to RC. In this regard, report from Al-Seraihy et al showed no correlation between relapse rate and MDS classification, which was comparable to other studies [13]. In addition to graft failure, infections secondary to immunosuppression from GvHD and its therapy were a major cause of non-relapse mortality in our patients, as shown in other series [25, 26, 27]. Cumulative incidence of acute GVHD was 37.1%, overall grade I a GVHD was seen in 53.8% while grade II was recorded in 46.2%. No severe grade III or above a GVHD was observed. The incidence of chronic GVHD was 21.2% in 33. 57.1% had extensive while the remaining in 42.9% it was limited. No severe acute GvHD was seen in our patients, this is due to utilization of intensive GvHD prophylaxis. Additionally, chronic GVHD was observed in a patient with a female adult donor, or among those with antigen mismatched donor HLA.

Donor type has always been considered as a major factor influencing the outcome following allogeneic HCT. Studies specifically addressing the role of HCT in children with MDS have indicated a probability of an EFS of about 50% following transplant with an HLA- matched family donor [25, 26], the same as obtained similar to what was observed in our series. The use of unrelated BM donors was associated with a higher incidence of acute and chronic GvHD, a higher transplant related mortality, and EFS probability of around 29% [28, 29]. Parikh et al [24] reported encouraging data regarding the use of UCB as a stem cell source for children with primary and secondary MDS achieving a three-year EFS of 60.9%, with a lower incidence of acute and chronic GVHD.

Conclusion

Although etoposide based conditioning was observed to be well tolerated yet, the Bu/Cy/±ATG conditioning regimen showed a trend of superiority for OS and EFS in our small series of patients undergoing HCT for MDS. The relapse incidence in our cohort was 11.5% in LR MDS group.

Authors' contributions/ Wkład Autorów

All authors were contributed to this manuscript by writing data collection, analysis and editing

Conflict of interest/ Konflikt interesu

The authors declare no conflicts of interest

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Ethics/Etyka

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform Requirements for manuscripts submitted to biomedical journals.

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