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Outcomes in patients undergoing hematopoietic stem cell transplantation for myelodysplastic syndromes

Sujith Karumathil, Uday Kulkarni, Sushil Selvarajan, Sharon Lionel, Anup J Devasia, Fouzia N Aboobacker, Kavitha M Lakshmi, Anu Korula, Alok Srivastava, Aby Abraham, Vikram Mathews, Biju George

Department of Clinical Haematology, Christian Medical College, Vellore, India

Abstract

Hematopoietic stem cell transplantation [HSCT] is the only curative option for patients with myelodysplastic syndromes [MDS]. Between 1991 and 2021, 154 patients [high risk, 86; low risk, 68] including 22 children underwent HSCT with a median age of 36 years. Conditioning regimens were myeloablative [n=97] and reduced intensity [n=53]. Donors were human leucocyte antigen (HLA)-matched related donors (MRDs) in 113 and alternate donors in 41. The graft source was peripheral blood stem cells in 92%.

Engraftment occurred in 126 [81.9%] at a median of 15 days while 20 [12.9%] died before engraftment and eight [5.2%] had primary graft failure. Sinusoidal obstruction syndrome was seen in 27 [17.5%]. Grade 2-4 acute graft versus host disease [GVHD] occurred in 46.3% while Grade 3-4 GVHD was seen in 34.9% and the incidence of chronic GVHD was 69.4%. Bacterial infections occurred in 38 (24.6%) while viral infections were seen in 31 [20.1%], mainly cytomegalovirus, and invasive fungal disease in 17.5%.

At a median of 33 months, 65 patients were alive; 14 (9.1%) had disease relapse, and 10 (6.5%) had secondary graft failure. The five-year overall survival (OS) (time from allogenic HSCT to death due to any cause) and event-free survival (time from allogenic HSCT to relapse/ progression of disease or death) were 41.69±4.2% and 40.8±4.4%, respectively. The five-year OS was significantly better in children [71%]. Outcomes were better with MRDs [45%] compared to alternate donors [29%; p=0.035]. Outcomes of HLA-MRD transplants have been improving; 44% for 1990 - 2000, 35% for 2001 - 2010, and 51% for 2011 - 2021. On multivariate analysis, age (adolescents and young adults [hazard ratio (HR) 2.7, p=0.021] and older adult age group [HR 3.6, p=0.006]), minor blood group mismatch [HR 2.0, p=0.028], bidirectional blood group mismatch [HR 2.6, p=0.010], and haploidentical stem cell donor [HR 2.2, p=0.007] were associated with poorer OS.

In conclusion, outcomes of HSCT for MDS are reasonable among matched sibling donors but outcomes in alternate donors require improvement. Strategies to reduce GVHD and infections should be explored.

Key words MDS, Stem cell transplantation, outcomes

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Correspondence: Biju George, Department of Clinical Hematology, Christian Medical College Vellore, Ranipet Campus. Ranipet District, Tamil Nadu, India. 632517, E-mail: biju@cmcvellore.ac.in

Introduction

Myelodysplastic syndromes (MDS) are a group of myeloid neoplasms characterized by clonal proliferation of hematopoietic stem cells, recurrent genetic abnormalities, myelodysplasia, ineffective haematopoiesis, peripheral-blood cytopenia, and a high risk of evolution to acute myeloid leukaemia (AML)[1] The treatment goals for patients with MDS are two-fold: improve peripheral blood indices (i.e., increase the hemoglobin level and reduce hemorrhage and infections) and change the natural progression of the disease[2]. Various prognostication systems have been used to guide risk stratification and therefore treatment options for MDS[3-5]. The most common are The International Prognostic scoring system [IPSS] and the Revised IPSS (R-IPSS). The IPSS-R classifies MDS into high risk (high and very high) and low risk (very low, low and intermediate) MDS. Low risk MDS is generally treated with growth factors, immune modulators or hypomethylating

agents, while high risk MDS is treated with hypomethylating agents, with or without allogenic hematopoietic stem cell transplantation [HSCT][6]. In patients with low risk MDS, HSCT is performed only if they have failed at least two to three lines of therapy; financial constraints to undergo allogenic stem cell transplantation are present; therefore, HSCT was only offered if the patients with low risk MDS failed at least two lines of therapy with patients arranging finance through various funds.

This dichotomy in treatment is based on the risk of progression to AML and the overall survival [OS][7-10]. With the advent of next generation sequencing, newer markers for disease classifications have been discovered, which assist in prognosticating the disease and in offering tailored therapy[11,12]. However in countries such as India, the patients are often referred late to appropriate hematology centres for correct diagnosis and appropriate management and are often misdiagnosed as cytopenia due to acute febrile illness, aplastic anemia or immune thrombocytopenic purpurea. In addition, the median age of patients diagnosed with MDS in India is usually less than 50 years; therefore, therapeutic options including HSCT become of paramount importance[13]. Our experience with HSCT for MDS from a single centre in India over a period of 30 years is presented.

Patients and Methods

This retrospective study analyzed patients who underwent allogeneic HSCT at the Christian Medical College, Vellore between July 1991 to December 2021. Only matched sibling donor [MSD] transplants were performed until 2009 and only from 2010, have matched unrelated donor [MUD] and haplo-identical [Haplo] transplants been performed for patients who do not have an MSD. This retrospective study is approved by the Institutional review board, Christian Medical College Vellore, India (Approval Number- 15702). All data were collected from individual medical records and institutional databases. Informed consent was only obtained at the time of HSCT and a separate consent was not obtained for this retrospective study.

Transplant

Myeloablative conditioning [MAC] and reduced intensity conditioning [RIC] regimens were used in patients with MDS. MAC regimens consisted of busulfan + cyclophosphamide (Tab busulfan 1 mg/kg/dose q6h for four days; Inj cyclophosphamide 60 mg/kg/day IV for two days), fludarabine + busulfan (Inj fludarabine: 40 mg/m^2 IV /day for four days; Inj busulfan: 130 mg/m^2/day IV for four days and dose adjustment made as per the therapeutic drug monitoring) or fludarabine +

Table 1. Baseline demographic data of patients undergoing HSCT for MDS

Baseline characteristics	Median (range) or Number (%) [n=154]
Median age [years]	36 (1-66)
Sex	
Male	106 [68.8%]
Female	48 [31.2%]
Median time from diagnosis to HSCT [months]	7 [1-240]
Number of lines of therapy prior to HSCT	
0	28 (18.2%)
1	93 (60.4%)
2	26 (16.8%)
3	7 (4.6%)
IPSS Score [n=138] ¶	
Low Risk	11 (7.9%)
Intermediate-1	50 (36.3%)
Intermediate-2	44 (31.9%)
High	33 (23.9%)
Data missing	16
Risk Status	
Low	68 (44.2%)
High	86 (55.8%)
Disease status at Transplant	
Complete remission	24 (15.7%)
Haematological Improvement	49 (31.8%)
With Disease	81 (52.5%)
Type of Conditioning Regimen	
Myeloablative	97 (62.9%)
Reduced Intensity	57 (37.1%)
Donor type*	
Matched Related	113 (73.3%)
Fully matched donor	106 (68.8%)
Mismatched donor	7 (4.5%)
Matched Unrelated	17 (11.1%)
Fully matched donor	4 (2.7%)
Mismatched donor	13 (8.4%)
Haploidentical	24 (15.6%)
Blood Group (mis) match	
No Mismatch	99 (64.3%)
Major mis match	23 (15%)
Minor mismatch	20 (13%)
Bidirectional mismatch	12 (7.8%)
Stem cell Source	
Bone marrow	11 (7.2%)
Peripheral stem cell	143 (92.8%)

HSCT, Hematopoietic Stem Cell Transplant; IPSS, International Prognostic Scoring System

¶ calculated based on IPSS. Even though Cytogenetic failure happened in 25 (15.2%) transplants, we were able to calculate risk status for 162 transplants as cytogenetic score will not alter the risk in the additional 22 transplants. We were not able to assign risk status in remaining three transplants as cytogenetic score will alter their risk.

*Fully matched donor-HLA identical donor; Mismatched Related-HLA mismatched (in only one locus-9/10) donor; Haploidentical-8/10 or 7/10 or 6/10 or 5/10 matched donor

treosulfan (Inj. fludarabine: 30 mg/m^2 IV/day for five days; Inj. treosulfan: 12 g/m^2 IV/day for three days). RIC regimens consisted of fludarabine + melphalan (Inj gludarabine: 30 mg/m^2 IV/day for five days; melphalan: 140 mg/m^2 IV for one day), fludarabine + cyclophosphamide (Inj. fludarabine: 30 mg/m^2 IV/day for six days; Inj cyclophosphamide 120 mg/kg/day IV for two days) or fludarabine + busulfan for two days (Inj fludarabine: 30 mg/m^2 IV/day for six days; Inj busulfan: 2.4 mg/kg/day IV for two days). The graft source was either bone marrow or peripheral blood stem cells [PBSC]. Graft versus host disease [GVHD] prophylaxis consisted of cyclosporine and short course methotrexate for MSD or MUD transplants; for MUD transplants, rabbit anti-thymocyte globulin [ATG] [4.5 mg/kg over three days] was added. Patients undergoing a Haplo HSCT received post-transplant cyclophosphamide [PTCy] 50 mg/kg on Days +3 and +4 followed by a calcineurin inhibitor [tacrolimus or cyclosporine] and mycophenolate mofetil starting Day +5. In the absence of GVHD, immunosuppression was generally tapered and stopped between Day 90-180.

Engraftment and toxicity

Neutrophil engraftment was defined as the 1st of three consecutive days with an absolute neutrophil count≥0.5 × 10^9/L. Platelet engraftment was defined as the 1st of seven consecutive days with a platelet count≥ 20 × 10^9/L without platelet transfusions for at least seven days. Chimerism analysis using variable number of tandem repeats was performed on Day 30 post-HSCT and repeated at 3, 6 and 12 months post-HSCT. Data on regimen-related toxicity including sinusoidal obstruction syndrome [SOS] (based on modified Seattle criteria[14]) and hemorrhagic cystitis was noted from medical records. Data on the presence of acute and chronic GVHD was also collected from individual medical records.

Antimicrobial prophylaxis and monitoring

All patients were nursed in HEPA filtered rooms. Fluconazole and acyclovir was started on Day +1 as antifungal and antiviral prophylaxis, respectively, but no anti-bacterial prophylaxis was given. Oral penicillin and co-trimoxazole-trimethoprim prophylaxis was added following recovery of blood counts and stable engraftment. For febrile neutropenia, antibiotics were administered as per prevalent institutional guidelines. High-resolution computed tomography scans of the chest and serum galactomannan were used to identify invasive fungal disease [IFD]. All patients were routinely monitored weekly for cytomegalovirus infection and urine was monitored every two weeks in alternate donor transplants for BK virus.

Statistical Analysis

Data was censored for analysis on 30th December 2022. OS included all patients who were alive at the final evaluation. Disease free survival [DFS] was calculated from the date of HSCT until death or relapse. For comparison of dichotomous variables, a chi-square test was performed while continuous variables were compared using either a Student's *t*-test or a Mann-Whitney *U*-test, as appropriate. The probability of OS and DFS were estimated using the Kaplan-Meier method. The prognostic relevance of clinical and biological variables was determined using univariate and multivariate Cox regression analysis. The covariates that were significant in the univariate analysis were used in the multivariate analysis and their significance was analysed using the enter method. Patients were stratified by IPSS and R-IPSS. For all tests, a two-sided p-value of 0.05 or less was considered statistically significant. Statistical analysis was performed using IBM SPSS 24.0 Software.

The primary outcome of this study was OS, and secondary endpoints included EFS, relapse incidence, non-relapse mortality, incidence of acute and chronic GVHD at any time during the follow up, incidence of documented infections (bacterial, viral, or fungal) from commencement of the conditioning regimen until the final follow up, graft failure (primary and secondary), and cause of mortality. Acute and chronic GVHD was diagnosed and graded as per established criteria[15,16].

Results

Between July 1991 and September 2021, 154 patients underwent allogeneic HSCT for MDS. Baseline characteristics are described in **Table 1**. Based on age, the cohort was divided into children (≤15 years of age); adolescents and young adults [AYA] (16-49 years of age)[17], and older adults (≥50 years of age). The median age of the cohort was 36 years [range: one to 66 years] and included 22 children [14.2%]. The majority [68.8%] were males. The median time from diagnosis to HSCT was seven months [range: one to 240 months]. Twenty-eight patients (18.2%) did not receive specific treatment prior to HSCT while 93 (60.4%), 26 (16.8%) and seven (4.6%) received one, two, or three lines of therapy, respectively, before HSCT (prior therapies include steroid, cyclosporine, danazol, hypomethylating agents, ATG, hydroxyurea and Imids) IPSS score analysis showed that 33 patients (23.9%) had a high risk IPSS score while 44 (31.9%) had Intermediate 2, 50 (36.3%) had Intermediate 1, and 11 (7.9%) had low risk scores. Sixteen patients did not have an IPSS score due to missing cytogenetic data or failure of cytogenetics. Overall, 86 (55.8%) had high risk MDS while 68 (44.2%) had low risk MDS. At the time of HSCT, 24 (15.7) were in

Table 2. Baseline characteristics across different donor types

Baseline characteristics	*Median (range) or Number (%)*			
	Matched Related n=113 (73%)	Matched Unrelated n=17 (11%)	Haploidentical 24 (16%)	*p value*
Total Number	113 (73.4%)	17 (11%)	24 (15.6%)	
Patient sex				0.746
Male	77 (68.1%)	11 (64.7%)	18 (75%)	
Female	36 (31.9%)	6 (35.3%)	6 (25%)	
Patient Age (in years)	37 (3-66)	37 (1-52)	29 (4-57)	0.134
Donor Age (in years)	37 (5-63)	33 (23-45)	36 (9-65)	0.490
Donor sex				0.142
Male	49 (43.4%)	11 (64.7%)	14 (58.3%)	
Female	64 (56.6%)	6 (35.3%)	10 (41.7%)	
Donor Recipient sex mis match	62 (54.9%)	10 (58.8%)	12 (50%)	0.848
Donor Recipient Blood group (mis) match				0.023
No Mismatch	79 (69.9%)	5 (29.4%)	15 (62.5%)	
Major Mismatch	15 (13.3%)	3 (17.6%)	5 (20.8%)	
Minor Mismatch	11 (9.7%)	6 (35.3%)	3 (12.5%)	
Bidirectional Mismatch	8 (7.1%)	3 (17.6%)	1 (4.2%)	
Number of lines of therapy prior to HSCT				0.243
0	24 (21.2%)	1 (5.9%)	3 (12.5%)	
1	69 (61.1%)	11 (64.7%)	13 (54.2%)	
2 or more	20 (17.7%)	5 (29.4%)	8 (33.3%)	
IPSS score				0.210
Low Risk	8 (8.2%)	2 (11.8%)	1 (4.2%)	
Intermediate-1	38 (39.2%)	5 (29.4%)	7 (29.2%)	
Intermediate-2	27 (27.8%)	4 (23.5%)	13 (54.2%)	
High	24 (24.7%)	6 (35.3%)	3 (12.5%)	
Disease status at Transplant				0.006
Complete remission	12 (10.6%)	3 (17.6%)	9 (37.5%)	
Haematological Improvement	41 (36.3%)	6 (3.3%)	2 (8.3%)	
With Disease	60 (53.1%)	8 (47.1%)	13 (54.2%)	
Type of Conditioning Regimen				0.001
Myeloablative	62 (59.4%)	17 (100%)	18 (75%)	
Reduced Intensity	51 (45.1%)	0 (0%)	6 (25%)	
Stem cell Source				0.285
Bone marrow	9 (8%)	2 (11.8%)	0 (0%)	
Peripheral stem cell	104 (92%)	15 (88.2%)	24 (100%)	
Stem Cell Dose (CD34 in 10^6/kg)	9.88 (1.04-33.1)	10.1 (1-13.4)	10 (4.76-17.1)	0.951

HSCT, Hematopoietic stem cell transplantation; IPSS, International Prognostic scoring system

complete remission, 49 (31.8%) had hematological improvement, and 81 (52.5%) with active disease received HSCT.

Transplant characteristics

The conditioning regimen was MAC in 97 (62.9%) patients and RIC in 53 (37.1%). The stem cell donor was a human leucocyte antigen-MRD in 113 (73.3%), a MUD in 17 (11.1%), and a Haplo donor in 24 (18.8%). Mismatched MSD or MUD transplants were performed in 20 [12.9%] patients. The graft source was predominantly PBSCs in 143 (92.8%) while bone marrow was used for 11 (7.2%) transplants. The blood group was identical in donor and recipient in 99 (64.3%) instances, major mismatch in 23 (15%), minor mismatch in 20 (13%), and bidirectional mismatch in 12 (7.8%). The baseline characteristics across the different donor types are shown in **Table 2**.

Engraftment, toxicity and infections

The median CD34+ dose infused was 10×10^6/kg (range: 1.04-33.1). One hundred and twenty-six patients [81.9%] were engrafted at a median of 15 days [range: 11-22]; 20 [12.9%] died before engraftment due to sepsis or SOS and eight [5.2%] had primary graft failure. The median time to a platelet count $>20 \times 10^9$/L was 18

days [range: 9-43]. Grade 3-4 mucositis was seen in 72 patients [46.7%]; it was significantly higher in patients having MAC compared to RIC [56.7% vs 29.8%; p= 0.001]. SOS was the most common regimen related toxicity [RRT] and it was seen in 27 patients [17.5%]. The incidence of SOS was not significantly different between MAC [16.4%] and RIC [19.2%] but there was a strikingly high incidence of the use of oral busulfan + cyclophosphamide [69.2%] compared to other regimens [fludarabine/melphalan, 19%; fludarabine/IV busulfan, 8.8%; cyclophosphamide/total body irradiation, and fludarabine/cyclophosphamide, 33%]. Other RRT included acute kidney injury in seven patients [4.5%], hemorrhagic cystitis and posterior reversible encephalopathy syndrome in three patients each [1.9%] and myopericarditis, subarachnoid hemorrhage and non-infective interstitial pneumonitis in one patient each.

Eighty-four patients [54.5%] had at least one documented infection (bacterial, viral, or fungal) requiring therapy. Blood stream bacterial infections occurred in 38 (24.6%) with majority of the infections [78.9%] caused by gram negative organisms. Viral infections were seen in 31 transplants [20.1%] with the majority being reactivation of cytomegalovirus. The incidence of IFD was 17.5% with a 12.5% incidence of proven/probable IFD.

Graft-Versus-Host-Disease

The incidence of Grade 2-4 acute GVHD was 46.3%; and the incidence of Grade 3-4 acute GVHD was 34.9% [**Table 3**]. The incidence was similar between MAC and RIC transplants [53.3% vs 58.3%, p=0.586]; however, bone marrow as the graft source was associated with a higher incidence of acute GVHD compared to PBSC [100% vs 52.1%; p=0.031], and MUD transplants had a higher incidence [84.6%] compared to MRD transplants [54.1%; p=0.036] and Haplo transplants [35.7%; p=0.009]. The overall incidence of chronic GVHD [among evaluable patients] was 69.4%, which was equally divided between localized and extensive chronic GVHD, respectively [30.5% vs 38.9%].

Survival

At a median follow up of 33.2 months (range: 0-270 months), 65 patients were alive while 89 died. Fourteen (9.1%) had relapse of disease while 10 (6.5%) had secondary graft failure. The median time to relapse was seven months [range: 3-195]. Relapse rates were significantly higher in patients with high risk MDS [15.1%] compared to low risk MDS [1.47%; p=0.003]. Relapses were higher in patients with persistent disease at the time of HSCT [12.3% vs 5.8%] although the difference was not statistically significant [p=0.117]. Of the 14 relapses, eight occurred as AML while six relapsed as MDS. Nine patients had a second transplant of whom only one is alive. The five-year OS for the entire cohort was 41.7 ± 4.2% (**Figure 1A**) and the five-year EFS was 40.8 ± 4.4% (**Figure 1B**). The five-year OS was significantly better in children [70.9 ± 1.0] compared to AYA [38.1% ± 5.1%] and older adults [28.7% ± 10.7%] (p=0.051) (**Figure 2A**). Outcomes were similar between low risk and high-risk disease [42.3 ± 6.4% vs 41.1 ± 5.6%; p=0.84]. Outcomes were better with the use of MRD [45.8 ± 4.9%] compared to alternate donors [MUD + Haplo] [29.4 ± 8.0; p=0.035] (**Figure 2B**). There was no difference in the outcomes between MUD and Haplo donors [31.4 ± 1.2% vs 31.2 ± 9.8; p=0.856]. The outcomes of MRD transplants have been gradually improving over the immediate recent years; 44.4 ± 1.6% for 1990 to 2000, 35.3 ± 8.2% for 2001 to 2010, and 51.3 ± 6.6% for 2011 to 2021 [p

Table 3. Transplant characteristics and outcomes

Baseline characteristics	Median (range) or Number (%)
CD 34 dose infused [×10^6/kg]	10 (1.04 - 33.1)
% Engraftment	126 (81.8%)
Time to ANC > 0.5×10^9/L (days)	15 (11 – 22)
Time to Platelet count > 20×10^9/L (days)	18 (9 – 43)
Graft Failure	18 (11.6%)
Primary	8 (5.1%)
Secondary	10 (6.5%)
Regimen related toxicity	
Grade 3-4 mucositis	72 [46.7%]
Sinusoidal obstruction syndrome	27 [17.5%]
Hemorrhagic cystitis	3 [1.9%]
Acute kidney injury	7 [4.5%]
Posterior reversible encephalopathy syndrome [PRES]	3 [1.9%]
Myopericarditis/Interstitial pneumonitis/SAH	1 [0.6%] each
Acute GVHD [no evaluable = 123]	
Overall Grade II – IV GVHD	56 (46.3%)
Grade III – IV GVHD	43 (34.9%)
Chronic GVHD [no evaluable = 95]	
Total	66 (69.4%)
Localised	29 (30.5%)
Extensive	37 (38.9%)
No of patients with documented Infection Total	84 (57.6%)
Blood stream bacterial infection	38 (24.6%)
Gram negative	30 (78.9%)
Gram positive	8 (21.1%)
Viral infections	31 (20.1%)
IFD – overall	27 (17.5%)
Proven and probable IFD	20 (12.9%)
Number of patients with relapse	14 (9.1%)

ANC, Absolute Neutrophil Count; SAH, Sub Arachnoid Hemorrhage; GVHD, Graft Versus Host Disease; IFD, Invasive fungal disease

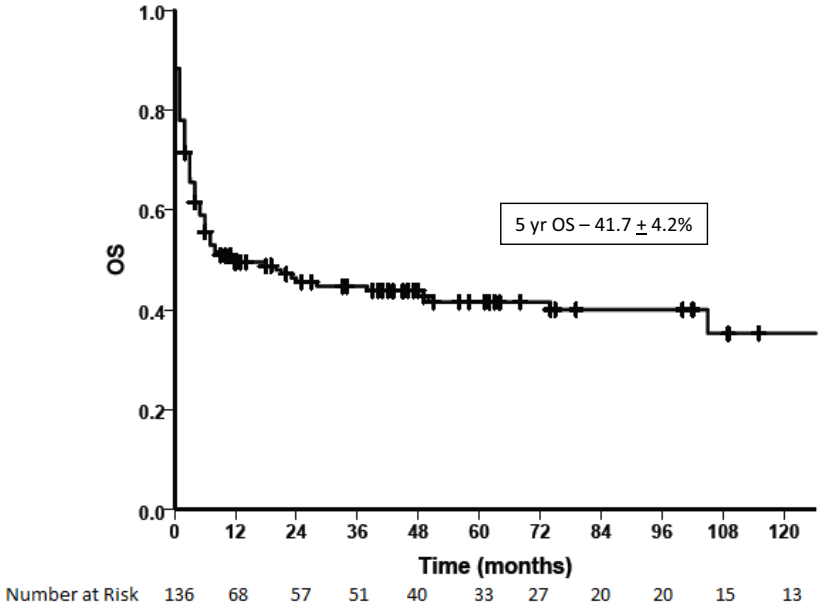

Figure 1A. Overall survival of patients undergoing HSCT for myelodysplastic syndrome

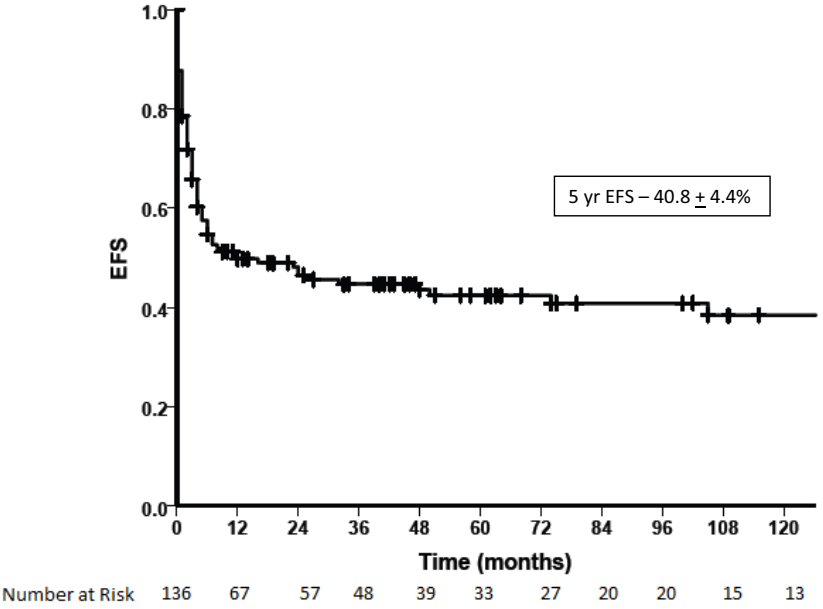

Figure 1B. Event free survival of patients undergoing HSCT for myelodysplastic syndrome

=0.092] (**Figure 3**). The main causes of mortality included bacterial sepsis [n=27; 30.4%], acute GVHD [n=19; 21.4%], graft failure [n=11; 12.4%], RRT [SOS, diffuse alveolar hemorrhage, subarachnoid hemorrhage, n=9; 10.2%], IFD [n=8; 8.9%], chronic GVHD [n=8; 8.9%], and relapse [n=7; 7.8%].

On univariate analysis, several pre-transplant factors including AYA [p=0.027], older adult age [p=0.032], minor blood group mismatch [p=0.017], bidirectional blood group mismatch [p=0.024], presence of active disease at HSCT [p=0.022], number of lines of prior treatment (one versus others) [p=0.029], and use of a Haplo donor [p=0.032] were associated with poorer OS. Sex, sex mismatch, major blood group mismatch, IPSS risk score, high versus low-risk disease, time from diagnosis to transplant, MUD, conditioning regimen, graft source, stem cell dose, and year of HSCT did not affect OS. On multivariate analysis, age (AYA [hazard ratio (HR) 2.7, p=0.021] and older adult age group [HR 3.6, p=0.006]), minor blood group mismatch [HR 2.0, p=

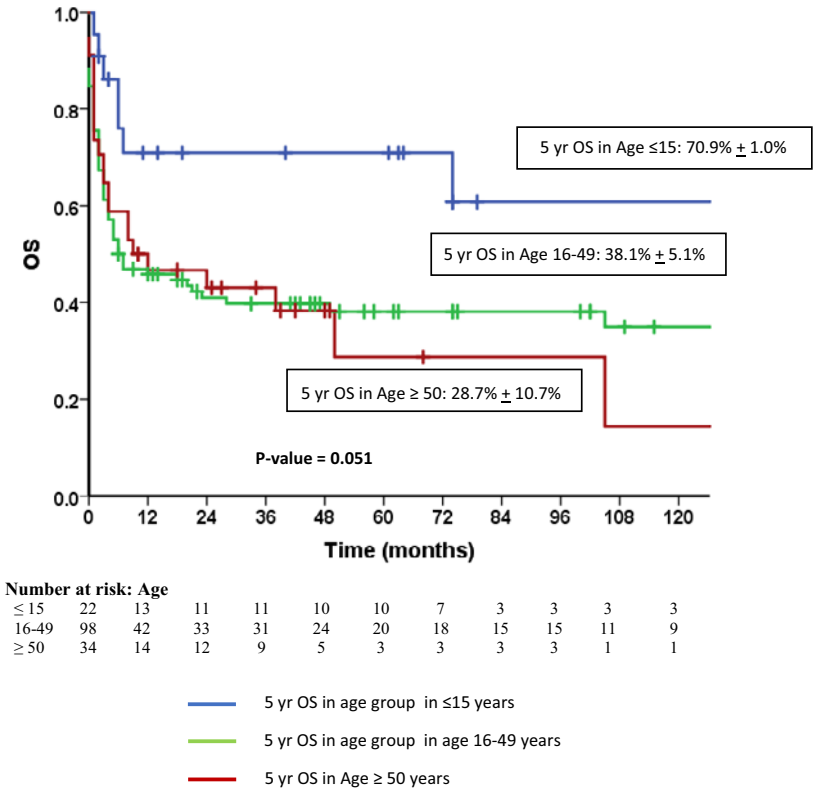

Figure 2A. Overall survival of children versus adults undergoing HSCT for MDS

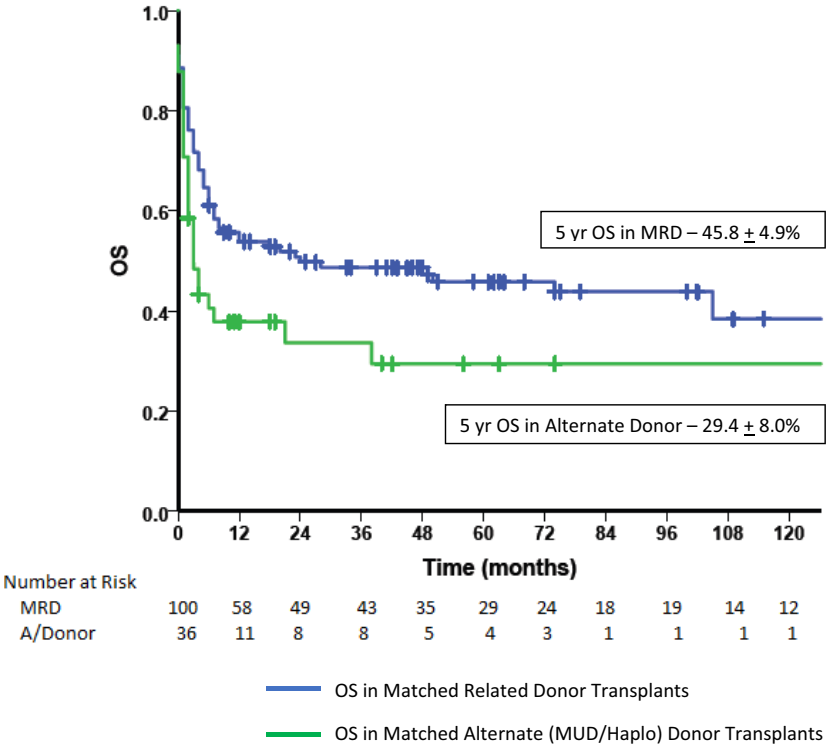

Figure 2B. Overall survival of matched related donor versus alternate donor HSCT for MDS

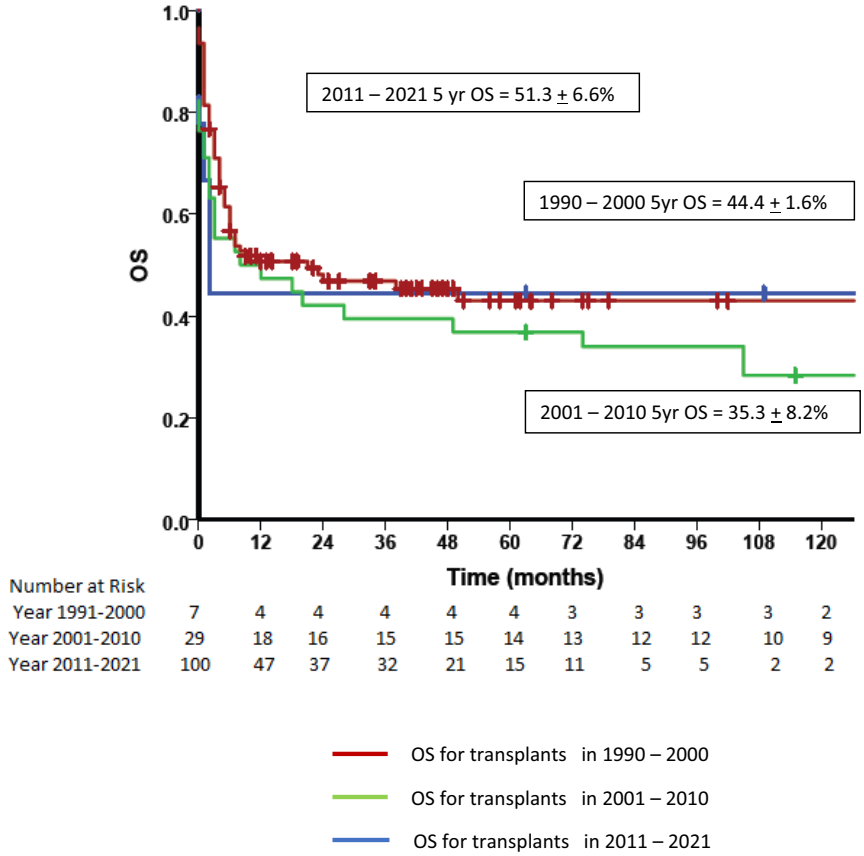

Figure 3. Overall survival of patients undergoing matched related donor HSCT for MDS

0.028], bidirectional blood group mismatch [HR 2.6, p= 0.010], Haplo donor [HR 2.2, p=0.007] continued to remain significant [**Table 4** and **Figure 4**].

Discussion

This single center study from India describes the outcomes of HSCT for patients with MDS over a 30-year period with a reported five-year survival of 42%. The outcomes were better in children [70%] compared to AYA [38%] and older adults [29%] (p=0.015) and with MRDs [45.8%] compared to alternate donors [30%; p= 0.035]. Even among MRD transplants, survival has been gradually improving with 51% survival reported in the cohort that underwent HSCT between 2011 and 2021 [51%], although the differences were not statistically significant. In the BMT CTN trial, with 1,102 prospectively enrolled patients with intermediate risk 2 and high risk MDS, the adjusted OS in the donor arm was 47.9%, similar to our cohort[10]. Our cohort is very different from most studies on HSCT in MDS since the median age of our cohort was 36 years, which is much lower compared to studies in Western countries where the median age is between 62-65 years[10]. Various studies from Asia have noted this age difference between cohorts of patients with MDS in Western countries and in Asia[13,18,19]. A higher number of patients [63%] received MAC because of the lower median age. The OS in children was 70%, similar to data reported by the EBMT[14]; however, the survival in younger and older adults only ranged between 35-36%. There are studies[25,26] showing variable outcomes in the AYA subgroup (OS varying from 47% to 71.2%) following allogenic stem cell transplant. This may be explained by the heterogeneity in clinical behavior of MDS. A recent proposal from a US group[27] highlights the requirement to implement a newer risk stratification scoring system for predicting post-transplantation outcomes in MDS. The outcomes of MSD transplants are reasonable with a 50% survival in those transplanted between 2011 and 2021; however, the outcomes of alternate donor transplants [MUD and Haplo] are low at 30%. A study from France comparing MSD and Haplo donors reported a two-year survival of 23.7% and a three-year survival of 19.8% in 48 patients undergoing Haplo transplant[21]. However, a study from the Adult Myelodysplastic Syndrome Working Group of the Japanese Society for Transplantation and Cellular Therapy comparing Haplo transplants with cord blood transplants have reported a two-year OS of 51%[22]. The Japanese data had patients who underwent cord blood transplantation along with Haplo patients and hence may not be entirely compara-

Table 4. Factors affecting overall survival in patients undergoing HSCT for MDS

Variables	Univariate analysis		Multivariate analysis	
	Risk [95%CI]	*p value*	Risk [95%CI]	*p value*
Age of patient				
≤ 15 years (Paediatric)	1.0		1.0	
16-49 years	2.4 [1.10-5.29]	0.027	2.7 [1.16-6.15]	0.021
≥ 50 years	2.5 [1.08-5.94]	0.032	3.6 [1.44-8.78]	0.006
Patient Sex: M	0.9 [0.61-1.50]	0.850		
Age of Donor	1.0 [0.99-1.03]	0.184		
Donor Sex	1.1 [0.74-1.70]	0.598		
Donor recipient sex (mis) match				
No Mismatch	1.0			
Sex Mismatch	1.0 [0.69-1.60]	0.832		
Donor recipient Blood Group (mis) match				
No Mismatch	1.0		1.0	
Major Mismatch	1.5 [0.87-2.70]	0.141	1.5 [0.87-2.77]	0.137
Minor Mismatch	2.0 [1.13-3.63]	0.017	2.0 [1.08-3.67]	0.028
Bidirectional Mismatch	2.2 [1.10-4.35]	0.024	2.6 [1.26-5.41]	0.010
Time from diagnosis to transplant	1.0 [0.99-1.00]	0.953		
Risk status at diagnosis [IPSS]				
Low Risk	1.0			
High Risk	1.2 [0.78-1.89]	0.389		
No. of lines of Treatment				
One	1.0		1.0	
Others	1.7 [1.06 – 2.77]	0.029	1.6 [0.94 – 2.78]	0.083
Disease status at HSCT				
CR + HI	1.0		1.0	
Active disease	1.7 [1.08 – 2.54]	0.022	1.3 [0.82 – 2.05]	0.274
Type of donor				
MRD	1.0		1.0	
MUD	1.3 [0.71 – 2.55]	0.369	1.2 [0.62 – 2.34]	0.584
Haploidentical	1.8 [1.05 - 3.22]	0.032	2.2 [1.24 - 3.97]	0.007
Type of Conditioning Regimen				
MAC	1.0			
RIC	0.9 [0.58 - 1.40]	0.626		
Stem cell source				
PBSC	1.0			
Bone Marrow	0.6 [0.28 - 1.19]	0.136		

IPSS, International Prognostic scoring system; HSCT, Hematopoietic Stem cell transplantation; CR, Complete response; HI, Haematological
Improvement; MRD, Matched Related Donor; MUD, Matched Unrelated Donor; MAC, Myeloablative conditioning; RIC, Reduced intensity conditioning; PBSC, Peripheral blood stem cell.

ble with our data. Also, their study period was between 2014 and 2020. Advances in alternate donor allogenic transplantation in recent years including PTCy, better GVHD control, and advances in antimicrobial control might have contributed to the superior OS than that in our cohort, which includes patients from 1991 to 2021.

The common causes of mortality included acute GVHD, bacterial infections and RRT along with relapse and graft failure. The OS in Grade I acute GVHD is 37.9 ± 14.1%; Grade II acute GVHD, 33.7 ± 24.8%; Grade III acute GVHD, 17.3 ± 8%; and Grade IV acute GVHD, 15.4 ± 10%. The rate of acute GVHD reported in this series was high at 55% with a 34% incidence of Grade 3-4 acute GVHD. Similar rates of 40 - 60% have been reported in other studies with the use of MAC and PBSC[10,22,23]. In addition, acute GVHD was one of the main reasons for the reduced OS; therefore, it is important to reduce this incidence although few studies have found that acute GVHD of any grade has no impact on OS[31,32]. Grade III-IV acute GVHD is associated with a poorer OS than with Grade I-II acute GVHD [p=0.001; HR, 3.02 (95% confidence interval: 1.58-5.78)]. How-

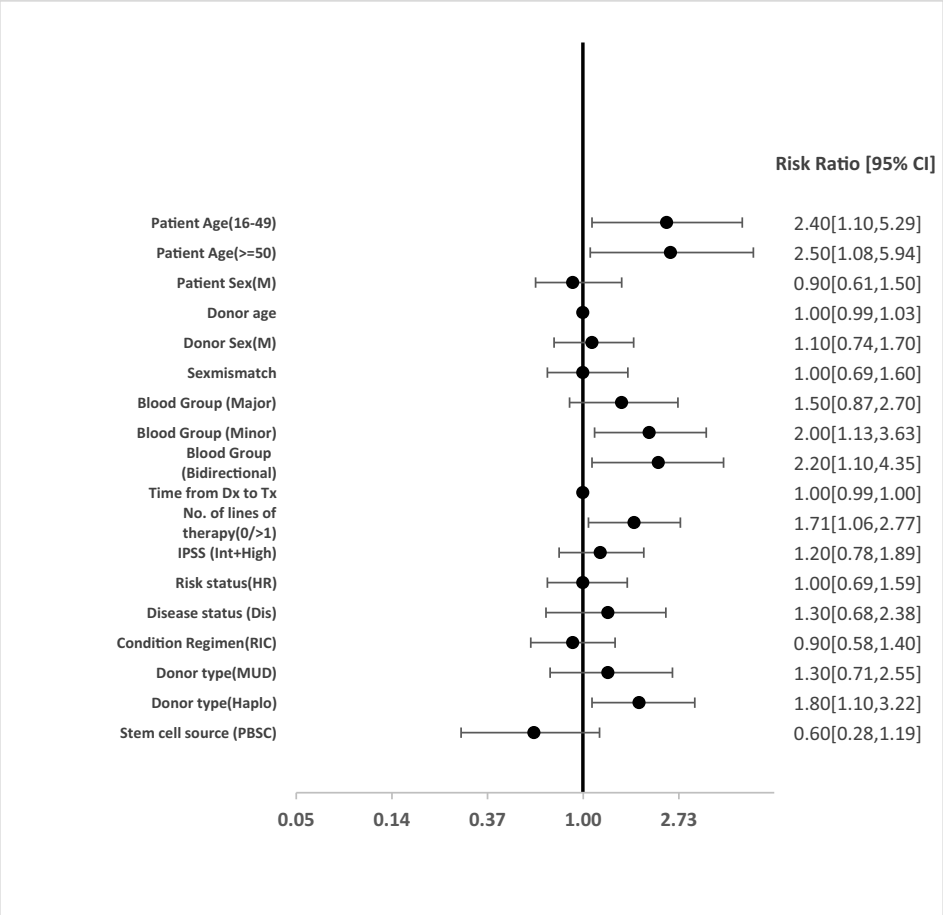

Figure 4. Factors affecting overall survival in patients undergoing HSCT for MDS, Forest plot
Forest plot showing variables and their impact on OS post-transplant. Patient age is in years. Based on IPSS score the patients were classified as having High Risk (HR) and low risk as mentioned as Risk status. Disease status (at transplant) denotes if patient had achieved haematological improvement (HI) or was having active disease (Dis).

ever, we found no survival advantage for Grade I acute GVHD compared with patients who had Grade II-IV acute GVHD (p=0.106). Multiple studies have shown that the addition of ATG to the conditioning regimen in patients undergoing MRD or MUD HSCT for MDS has been associated with low rates of GVHD, although it had no impact on OS[28-30,33]. A few studies have explored the use of PTCy as GVHD prophylaxis in the setting of MSD and MUD transplants with low rates of GVHD[34,35].

Bacterial infections continue to remain a major problem among allogeneic transplant recipients in India and is one of the risk factors identified with poorer OS in patients undergoing HSCT for MDS[36]. Early initiation of antibiotics in patients at high risk of bacteremia due to multidrug resistant organisms [MDRO] has been one of the strategies that have been employed in these patients for the past three to four years and a detailed analysis is ongoing to understand if this strategy has been successful in reducing mortality due to MDRO sepsis.

Since we have a young cohort of patients with MDS, MAC has been commonly used. Initially busulfan + cyclophosphamide was used but it was associated with high rates of SOS and subsequent mortality. Since 2010, we have been using fludarabine + busulfan as the standard conditioning protocol with a reduced incidence of SOS. The ideal conditioning regimen for young and old patients has not yet been defined. Few studies have shown that the use of treosulfan instead of busulfan was associated with lower toxicity but similar survival[37]. We have recently shown that total marrow lymphoid irradiation is associated with low toxicity in patients with acute lymphoblastic leukemia undergoing allogeneic HSCT and we plan to further explore if this can be used in MDS, based on data that is available in myeloid malignancies that are refractory and in remission[38-41].

There has been conflicting data regarding the impact on OS of blood group mismatch between a donor and the recipient[42-44]. In the current study we found that major blood group mismatch had no impact on OS but minor and bidirectional mismatch had worse impacts on

OS.

Approximately 44% of our patients had lower risk MDS, and at our centre an allogeneic transplant was considered if at least two lines of treatment had failed. However, it is important to note that many of the drugs that are currently available for low-risk MDS are, unfortunately, unavailable in India or are too costly for routine use, and also, because of the relatively younger age of our patients, many prefer to choose a curative procedure such as an allogeneic transplant. The OS in this group was 42%, which is lower than the reported rates of 50 to 58% by different groups, including the European Society for Blood and Marrow Transplantation (EBMT)[45-47]. Changes in conditioning regimens and the addition of ATG to the conditioning should be considered to improve outcomes in this group of patients[28,33,48].

In summary, this analysis shows that HSCT in MDS is associated with improving outcomes among MSDs; however, outcomes in Haplo and MUD transplants are poor and require improvement. GVHD and infections are the major causes of mortality, and strategies to reduce both should be incorporated into conditioning protocols to improve the outcomes of HSCT for MDS.

Author Contributions

SK is involved in collecting the data. BG, SK and UPK are involved in conceptualisation and coordination of this work. BG, KML and SK did the statistical analysis. All authors reviewed the manuscript for important intellectual content, approved the final manuscript, and agreed to be accountable for all aspects of this work.

Conflicts of Interest

The authors declare no conflict of interest. Disclosure forms provided by the authors are available on the website. AS is one of the editors of Blood Cell Therapy. He was not involved in the editorial evaluation or decision to accept this article for publication.

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