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Cytogenetics, Donor Type and use of Hypomethylating Agents in Myelodysplastic Syndrome with Allogeneic Stem Cell Transplantation

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Abstract

We investigated the impact of patient and disease characteristics including cytogenetics, previous therapy and depth of response on the outcome of allogeneic hematopoietic stem cell transplantation (HSCT) on myelodysplastic syndrome (MDS). We analyzed 256 MDS patients transplanted from a matched related (n = 133) or matched unrelated (n=123) donor after 2001. Of 256, 78 (30.5%) did not receive cytoreductive therapy before HSCT; 40 (15.6%) received chemotherapy (chemo), 122 (47.7%) hypomethylating agents (HMA) and 16 (6.2%) both (chemo +HMA). Disease status at HSCT defined by International Working Criteria was complete remission (CR) in 46 (18%) patients. There were significant differences between therapy groups: There were more therapy-related MDS and the use of MRD in the untreated group. The chemo group had higher serum ferritin levels at HSCT. Patients were older and had more high-risk disease by revised international prognostic scoring (r-IPSS) in the HMA group. Despite those differences, transplant outcomes were similar in patients who were untreated and who received cytoreductive therapy prior to HSCT. Three-year EFS was 44.2%, 30.6%, 34.2% and 32.8% for untreated, chemo, HMA and chemo+HMA groups respectively (p=0.5).

Multivariate analyses revealed that older age (HR=1.3, p=0.001); high-risk histologic subtypes including refractory anemia with excess blasts (HR=1.5, p=0.05) and chronic myelomonocytic leukemia (HR=2.1, p=0.03); high risk cytogenetics with MK (HR=4.0, p<0.0001) and high serum ferritin level at HSCT (HR=1.8, p=0.002) were poor prognostic factors for EFS. Bone marrow blast count 5% or higher at HSCT (HR=1.6, p=0.01) and MK (HR=4.2, p<0.0001) were the only

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prognostic factor for increased relapse incidence after HSCT. Patients with MK represented a poor prognostic group with 3-year LFS of 11.4% and RI of (RI) of 60.9%.

In this analysis, various therapy approaches prior to HSCT did not lead to different transplant outcomes. Cytogenetics defined by MK was able to identify a very poor prognostic group that innovative transplant approaches to improve outcomes are urgently needed.

INTRODUCTION

Myelodysplastic syndromes (MDS) compose a family of clonal hematopoietic diseases characterized by bone marrow failure and a predisposition to evolve into acute myeloid leukemia (AML)[1]. Despite major progress in the understanding of its pathophysiology and recent advances in treatment, particularly with hypomethylating agents (HMAs), MDS remains incurable with standard forms of treatment. Allogeneic hematopoietic stem cell transplantation (HSCT) is the only therapeutic option that has the potential to produce long-term remission, with disease-free survival of 25–60% depending on disease characteristics [2–4]. The major cause of treatment failure after HSCT in MDS is relapse of the disease. Cytogenetic abnormalities and the proportion of bone marrow myeloblasts are known to predict for the risk of relapse after HSCT. Cytoreductive therapy is commonly used before referral for HSCT with a goal to reduce the risk of disease relapse post-transplant. The effectiveness of chemotherapy and/or HMA treatment prior to HSCT is not established.

In the present analyses, we sought to determine the impact of disease characteristics at diagnosis and at HSCT including pre-transplant MDS therapy and depth of response, cytogenetics and donor type on the outcome of HSCT.

METHODS

Patient population

We retrospectively analyzed 256 patients 18 years or older who were diagnosed with MDS and underwent first HSCT at the University of Texas MD Anderson Cancer Center from January 1, 2001, to December 31, 2012. Histological subtypes were classified according to the World Health Organization (WHO) definition[5]. Forty patients (15.6%) with refractory anemia (RA) or RA with ringed sideroblasts (RARS) and 34 (13.7%) with refractory cytopenia with multilineage dysplasia (RCMD/RCMD-RS) were grouped as “low/intermediate risk” histology while 45 (17.6%) with RA with excess blasts, type 1 (RAEB-1), and 55 (21.5%) with RAEB-2 were grouped as “high-risk” (Table 1). The histological subtype was MDS-unclassifiable (MDS-U) in 59 cases (23.2%), and 23 patients (9%) had chronic myelomonocytic leukemia (CMML). Cytogenetic findings were classified according to the 5-group classification recently described by Schanz et al.[6] (Supplementary data, Table 1) and monosomal karyotype (MK) reported by Breems et al.[7]. Patients were categorized by revised International Prognostic Scoring System (IPSS-R) by disease characteristics at diagnosis[8]. CMML and therapy related MDS (t-MDS) were not included in this risk scoring per definition.

Prior therapy for MDS and response evaluation

Of the 256 patients included in the study, 178 (69.5%) received treatment for MDS using chemotherapy and/or hypomethylating agents (HMA) prior to HSCT while 78 (30.5%) received only best supportive and categorized as “untreated”. Patients who received cytoreductive therapy were further categorized by the treatment received: 40 (15.6%) only chemotherapy (chemo), 122 (47.6%) only HMA and 16 (6.3%) both chemotherapy and an HMA (chemo+HMA) prior to HSCT. Disease status at HSCT was defined by International Working Group (IWG) criteria[9] for patients who received prior therapy for MDS.

HSC allograft characteristics

The source of hematopoietic stem cells (HSC) was peripheral blood (PB) in 169 patients (66%) and bone marrow (BM) in 87 patients (34%). Serologic or low-resolution molecular techniques were used for class I antigens and high-resolution molecular typing using polymerase chain reaction for class II alleles for human leukocyte antigen (HLA) typing until July 2005. After July 2005, all donors had high-resolution molecular typing of class I and II antigens. Of 256, 133 (52%) had matched unrelated donors (MUD) that were classified based HLA typing as described by Weisdorf et al[10]. The rest had matched related donor (MRD).

Conditioning regimens varied but were fludarabine and busulfan based in 195 (76.2%) or fludarabine and melphalan based in 61 (23.8%) patients. The impact of conditioning regimens on outcomes was analyzed by their dose intensity, using Center for International Bone Marrow and Transplantation Center (CIBMTR) criteria for reduced intensity vs. myeloablative preparative regimens[11]. Of 94 patients with RIC, 55 (58.5%) were age 60 or older in contrast to 31 of 162 (19.1%) patients with MAC ($p<0.001$). Tacrolimus and methotrexate were used as graft-versus-host disease prophylaxis in the majority of the patients (90.7%). Treatment protocols and this retrospective analysis were approved by the University of Texas-MD Anderson Cancer Center Institutional Review Board. All patients provided written informed consent for the treatment.

Endpoints and definitions

The primary endpoints were relapse incidence (RI), transplant-related mortality (TRM), event-free survival (EFS) and overall survival (OS). All outcomes were measured from the time of stem cell infusion. Relapse was defined as hematologic recurrence of MDS according to standardized criteria (9). TRM was death because of causes other than relapse of MDS. For analyses of EFS, treatment was considered a failure at the time of relapse or at the time of death from any cause; data for patients who were alive and in CR were censored at the date of last contact. OS was based on death from any cause; surviving patients were censored at the date of last contact. Cumulative incidence was used to estimate the endpoints of RI and TRM. EFS and OS were calculated using the Kaplan-Meier method. Univariate comparisons of all end points were completed by the log-rank test. A Cox proportional hazards model (12) or the Fine & Gray method (13) for competing hazards was used for multivariate regression. Variables were included in the multivariate model if they were conceptually important or if they approached ($p<0.10$) or attained statistical significance in

the univariate regression. All factors were tested for the proportional hazards assumption. Analyses were performed using STATA System for Windows version 11.2.

RESULTS

Patient and disease characteristics of the study cohort and by each pre-transplant MDS therapy approach are presented in Table 1. The median age at HSCT was 56 years (interquartile range (IQR), 48–62 years) and 86 patients (33.6%) were age 60 or higher. Our study cohort had high-risk features including 92 patients (35.9%) with t-MDS and 100 (39.1%) with high risk histology. Fifty-nine of 144 patients (40.1%) evaluable for IPSS-R were in high or very high-risk group by r-IPSS at diagnosis. At HSCT, the median BM blast count was 3% (IQR, 1–7), and 39 patients (15.3%) had a blast count of 10% or more. The median pre-transplant ferritin level was 1131 μg/L (IQR,521–2334). The median time from MDS diagnosis to HSCT was 8 months (IQR, 5.2–15.3 months).

There were differences observed between therapy groups. Patients who received HMA prior to HSCT were older and had more high or very high risk disease by r-IPSS compared with the rest of the cohort. Patients who received chemotherapy had a higher serum ferritin level at HSCT. Untreated patients had a greater proportion of therapy related MDS and MDS-U at diagnosis and proceeded with HSCT within a shorter period of time after diagnosis, and more often with a MRD. There was also a difference in the date of transplant between therapy groups. Of 62 patients transplanted before2005, 36 was untreated (58.1%) and the rest received chemotherapy only. After 2005, when HMA became available, of 194 transplanted MDS patients, only 42 were untreated (21.7%) and 14 (7.2%) received chemotherapy only. Majority of the patients, 122 of 194 (63.4%) received only HMA after 2005.

Cytogenetic abnormalities

Approximately half of the cohort had high risk cytogenetics (Table 1). MK and 5-group cytogenetic classification overlapped significantly since 63 of 73 (86.3%) MK positive (MK +) patients were in “very poor” group and all normal cytogenetics (CN) were in “good” risk groups ($p<0.001$). Among 96 MK negative (MK-) patients, 20 (20.8%) was in “good”, 32 (33.3%) in “intermediate”, 36 (37.5%) in “poor” and 8 (8.3%) in “very poor” risk groups by 5-group cytogenetic classification. Complex karyotype (CK) was also significantly associated with MK as 66 of 73 of MK+ patients (90.4%) had CK ($p<0.0001$).

The distribution of high risk cytogenetics were similar between low/intermediate and high risk histology groups ($p=0.1$). However CMML was different; 13 of 23 (56.5%) had CN and only 1 patient had MK+. Of 92 t-MDS patients, 36 (39.1 %) had MK− and 44 (47.8%) had MK+ while 60 (37%) and 29 (17.9%) of the rest had MK− and MK+ respectively ($p<0.001$).

MDS Therapy prior to HSCT

178 patients received MDS therapy prior to HSCT. 46 (25.8%) achieved complete remission (CR), 29 (16.3%) marrow CR, 63 (35.4%) stable disease (SD) and in 40 (22.5%) progressive disease (PD) prior to hematopoietic transplantation. Patients not in CR were grouped together as active disease (AD) at HSCT. There was no difference among different therapy

groups to achieve CR at HSCT (p=0.7). Similarly, the rate of CR at HSCT was comparable in different cytogenetic risk groups. By IWG criteria, 18.9% of CN, 14.9% of MK− and 21.9% of MK+ patients were in complete remission (p=0.3).

The persistence of the abnormal cytogenetic clone at HSCT was evaluated in 113 patients who had cytogenetic abnormalities and received MDS therapy prior to HSCT. Of these 113, 106 were evaluable for cytogenetic response; 35 (33%) had a normal karyotype at transplantation while 71 (67%) had persistence of the abnormal clone detected at diagnosis. There was no difference among different therapy groups in achieving cytogenetic remission (p=0.6). Similarly, the rate of cytogenetic remission after MDS therapy at HSCT was comparable in different cytogenetic risk groups; 32.1% MK− and 30.8% of MK+ patients were in cytogenetic remission at HSCT (p=0.8).

Disease Outcomes

Overall 112 patients were alive at last follow up with a median survival of 34 months (IQR, 17–63 months). 100 (89.3%) were alive and free of disease at their last follow-up. RI was 34.1% at 3 years (95% confidence interval (CI), 28.0%−40.2%) and most relapses occurred within the first year after HSCT with an incidence of 27.7% (95%CI, 22.4%−33.3%). The incidence of TRM at 3-year was 29.3% (95%CI, 23.5%−34.3%). Three-year EFS and OS were 36.6% (95%CI, 30.3%−43%) and 41.6% (95% CI, 34.9%−48.1%) respectively.

Univariate Analyses

Relapse and TRM—As summarized in Table 2, high-risk histology, high risk cytogenetic defined by any of the 2 classifications schemas at diagnosis, as well as BM blast count of 5% or greater at HSCT was associated with increased risk of relapse (Table 2). Significant prognostic factors for increased TRM were older age, serum ferritin levels > 1130 μg/L at HSCT and the use of MUD versus MRD. The use of a RIC conditioning regimen, which was significantly associated with older age (p<0.001), was also found to increase TRM. HSCT after 2005 did not decrease TRM significantly in univariate analysis.

Event Free Survival: The median EFS was 12.6 months (IQR, 3.6-not reached (NR)). Older age, high-risk histology, t-MDS, high risk cytogenetic defined by any of the 2 classifications schemas at diagnosis, BM blast count of 5% or higher and serum ferritin levels > 1130 μg/L at HSCT were associated with decreased EFS. MK was able to identify 3 different risk groups for EFS while 5-group identified two risk groups. HSCT after 2005 was associated with improved EFS but that did not reach statistical significance.

Overall Survival: The median OS was 20.1 months (IQR, 6.3-NR). Older age, high-risk histology, t-MDS, BM blast count of 5% or higher and serum ferritin levels > 1150 μg/L at HSCT were also associated with inferior OS. Transplant with a MUD had decreased OS compared with use of a MRD. Similar to EFS, monosomal karyotype was able to identify 3 different risk groups for OS while 5-group cytogenetic classification identified two risk groups (Table 2). HSCT after 2005 was associated with improved OS but that did not reach statistical significance.

The impact of previous therapy on HSCT outcomes

The transplant outcomes were similar between different therapy groups including untreated patients (Table 2). Similarly, patients in CR and AD at HSCT following MDS therapy and untreated patients had similar RI, TRM, EFS and OS. Focusing on the 144 patients who had BM blasts, 5% or higher at any time point during the course of their disease, we compared 34 patients in CR at HSCT with 86 who had AD and 24 untreated patients. Patients with AD at HSCT had increased TRM (HR= 2.6 p=0.03) while RI (HR=0.6, p=0.2), EFS (HR=1.2, p=0.4) and OS (HR=1.5, p=0.1) were not statistically different compared with those transplanted in CR. All transplant outcomes including TRM (HR=1.4, p=0.5), RI (HR=0.7, p=0.4), EFS (HR=0.9, p=0.8) and OS (HR=1.0, p=0.9) were comparable for patients that were untreated compared with CR patients. Among 112 patients that never had BM blast count 5% or higher during their disease course, we did not observe any difference for any transplant outcomes between 13 patients in CR at HSCT, 47 who had AD and 54 untreated patients.

Similar to morphologic response to MDS therapy, cytogenetic remission among patients with cytogenetic abnormalities did not lead to superior outcomes compared to those with persistence of the abnormal cytogenetic clone. We did not observe a difference in RI, TRM, EFS and OS between patients with and without persistence of the abnormal cytogenetic clone (p=0.6, p=0.9, p=0.2, p=0.1 respectively).

The impact of donor type and year of transplant on HSCT outcomes

In our cohort, all unrelated donors had high-resolution molecular typing of class I and II antigens after July 2005. To investigate the impact of better allele level matching on MUD transplant outcomes, we used the transplant year (before 2005 vs. after 2005) as a surrogate marker. MRD patients served as a control group since they had no change in HLA typing and selection algorithm over the same time period.

TRM at 3 years improved from 53.4% to 34.9% after 2005 for MUD (HR=0.6, p=0.1) while no improvement was observed for MRD patients; 3-year TRM was 26.8% before 2005 and 21.7% after 2005 (HR=0.8, p=0.5). For MUD, significant improvements for both EFs and OS were observed after 2005; the 3-year EFS increased from 17.7% to 37.9% (HR=0.6, p=0.06) and 3-year OS from 17.7% to 39.9% (HR=0.5, p=0.03). For MRD, 3-year EFS increased from 32% to 41.2% (HR=0.8, p=0.3) and 3-year OS from 38.7% to 50% (HR=0.8, p=0.3); those differences were statistically not significant.

Multivariate analyses

Multivariate models confirmed the role of high risk cytogenetic defined as MK+ or very high risk by 5-risk group classification on RI, EFS and OS (Figure 1a-b). In Table 3, we presented the models with MK due to its potential to identify 3 risk groups for all EFS and OS in a linear fashion. Among patient and disease characteristics, older age, high-risk cytogenetics with MK+, histological subtype of CMML and high serum ferritin level at HSCT decreased both EFS and OS compared with low/intermediate risk histology and low serum ferritin level at HSCT respectively. MK+ also was a poor prognostic factor for relapse incidence as BM blast count of 5% or higher at HSCT was. Among transplant related

variables, the use of MUD was associated with increased TRM and decreased OS. HSCT after 2005 was associated with decreased TRM and improved EFS and OS significantly.

DISCUSSION

Our study, conducted at a single center with a relatively large cohort of MDS patients, demonstrates important findings that 1) High risk cytogenetic abnormalities at diagnosis determine prognosis after HSCT 2) unrelated donor transplants have inferior OS and higher TRM compared with transplants from a matched related donor and, and 3) in patients treated with HMAs and/or chemotherapy and have not progressed to AML, response to treatment prior to HSCT may not affect post-transplant outcomes.

One of the most striking findings in the present study was reliable and reproducible identification of a very poor prognosis group by the MK classification[7], which was developed for the prognostication of non-transplanted AML patients, and the 5-group classification developed for primary MDS patients [6]. MK+ patients comprised a very high-risk group with 3-year RI of 60.9%, EFS of 11.4% and OS of 15.8%. This is in contrast to good risk CN patients with 3-year RI of 16.9%, EFS of 62.3% and OS of 65.1%. MK− patients comprised an intermediate-risk group with 3-year RI of 26.7%, EFS of 30% and OS of 38.8%.

The presence of MK+ cytogenetic abnormalities has been associated with poor prognosis in patients with MDS [12,13]. Similar to our findings, recent reports also suggested that patients with MK+ also have increased risk of relapse with increased mortality post transplant[14,15]. The Spanish Registry for MDS[16] reported a strong association of MK with complex karyotype and suggested that it is the complexity of the karyotype (ie, number of chromosomal abnormalities) that is prognostic for worse outcomes in MDS. In our cohort, we could not test that hypothesis owing to the small number of MK+ patients without CK abnormalities. Our results and other reports suggest that MK and the 5-group cytogenetic risk classification schemas are more predictive for post-transplant outcomes than IPSS cytogenetic classification in MDS patients.

We showed that unrelated donor transplants had inferior OS and higher cumulative incidences of TRM compared with transplants from matched related donors. These results are surprising considering the comparable outcomes reported for MUD with MRD in AML patients [17,18]. Recently, a CIBMTR analysis with 701 MDS patients transplanted between 2002 and 2006 also showed similar findings and reported 10%−20% lower rates of OS with MUD and 7/8 MUD compared with MRD patients. They also showed no difference in the incidence of relapse but TRM was increased in MUD patients compared with MRD[19]. The selection criteria for MUD have changed over the years and that should lead to an improvement in MUD outcomes. When we looked at our results after 2005, the year we started high-resolution molecular typing for both class-I and class-II antigens, we observed a decrease in the difference between MUD and MRD transplants. While the 3-year OS was 20% inferior with MUD compared with MRD before 2005, this difference was down to 10% after 2005. These data suggest that donor type should be considered while planning HSCT,

but unrelated donor transplants do offer an opportunity for long term survival in selected patients with high risk MDS especially with strict matching criteria.

We did not observe different outcomes after various therapy approaches prior to HSCT. The untreated group was unique that it included mostly t-MDS patients who were closely monitored for other hematologic malignancies and underwent HSCT mostly with a MRD within a median of 5 months after MDS diagnosis. Among the patients who had MDS therapy prior to HSCT, the 122 patients who received only HMAs were older and had more high risk groups by r-IPSS. Despite those poor prognostic features, the HMA group had similar post-transplant outcomes compared with the chemo group, a finding similar to those presented in a recent report by Damaj et al[20]. More importantly, despite the significantly older age of patients in the HMA cohort, TRM was not higher than observed in younger patients of the untreated group. Therefore, our results and previously published data [20–23] support the notion that using HMA in MDS patients prior to HSCT is a valid therapeutic approach that renders RI, EFS and OS similar to those achieved by chemotherapy.

In this analysis, cytoreduction with any therapy approach to achieve CR did not lead to improved RI, EFS or OS. Even achievement of a deeper level of remission with normal karyotype at transplantation was not associated with decreased RI and improved survival in patients with cytogenetic abnormalities at diagnosis. Our results were interesting that BM blast count ≥5% at HSCT was a poor prognostic factor for relapse in addition to high risk cytogenetics in the multivariate model although that was not for OS and EFS. One should remember that CR criteria by IWG is a very strict one and effective cytoreduction may not be associated with achieving CR in all the cases. In our cohort, the patients who had previous MDS therapy had a median BM blast count of 3% at HSCT but only 25% of those were in CR. These results, although must be interpreted with caution due to limitations inherent in retrospective study design, are unable to answer the question of the overall benefit of MDS therapy prior to HSCT but also do not show an advantage of pretranplant therapy.

The value of prior cytoreductive therapy is still not clear in the absence of randomized trials. A randomized study, from the European Group for Blood and Marrow Transplantation, had to be stopped because of slow recruitment. Retrospective single-center studies failed to show definitive evidence of a survival benefit associated with chemotherapy therapy before HSCT, with additional selection bias as a result of the difficulty accounting for patient drop-out (ie, patients who received induction chemotherapy but never received HSCT because of death ortoxicity)[24,25]. Whether treatment with HMA, which has a good toxicity profile, prior to HSCT xoffers an advantage also remains to be established. In recent analyses, there was no benefit to HMA when HMA was compared with no treatment before HSCT[21]. Similarly, patients with response and/or less than 5% bone more blast after HMAs did not have improved transplant outcomes compared with non-responders[20,26]. Despite the paucity of data showing improvement of survival after HSCT, pre-transplant therapy is commonly used. In our series, approximately 80% of our patients received HMA prior to transplant after 2005 when HMAs became available. Given the risk of losing transplant eligibility as a result of dearth or treatment related toxicity, HMAs can be a better option compared with chemotherapy for patients in whom transplantation is contemplated. On the other hand, ours

and previous results suggest that not only cytoreductive therapy should be further addressed in prospective controlled clinical trials but also the paradigm of treatment selections in MDS patients may need to change. Considering the aim of pretransplant cytoreductive therapy is to decrease relapse and improve survival, other strategies of intensifying conditioning regimen[27] and post-transplant maintenance[28] with recent encouraging outcomes should be explored further.

In conclusion, this analysis shows MK and the 5-group cytogenetic classification can better define prognostic groups for OS, EFS, and RI than IPSS cytogenetic classification after HSCT. Patients with MK+ or "very poor" cytogenetic with poorer prognosis after HSCT should be the target of future studies with innovative strategies to improve transplant outcomes. In this analysis, we could not demonstrate a benefit of pretransplant cytoreductive therapy using HMA or chemotherapy on the outcome of hematopoietic transplantation. Prospective controlled trials are needed to address optimal initial management of patients with MDS who are candidates for hematopoietic transplantation. Until that data is available, given the acceptable toxicity, potential for cytoreduction and acceptable transplant-related mortality, HMAs may have an advantage over chemotherapy for MDS patients that are transplant candidates and need further therapy.

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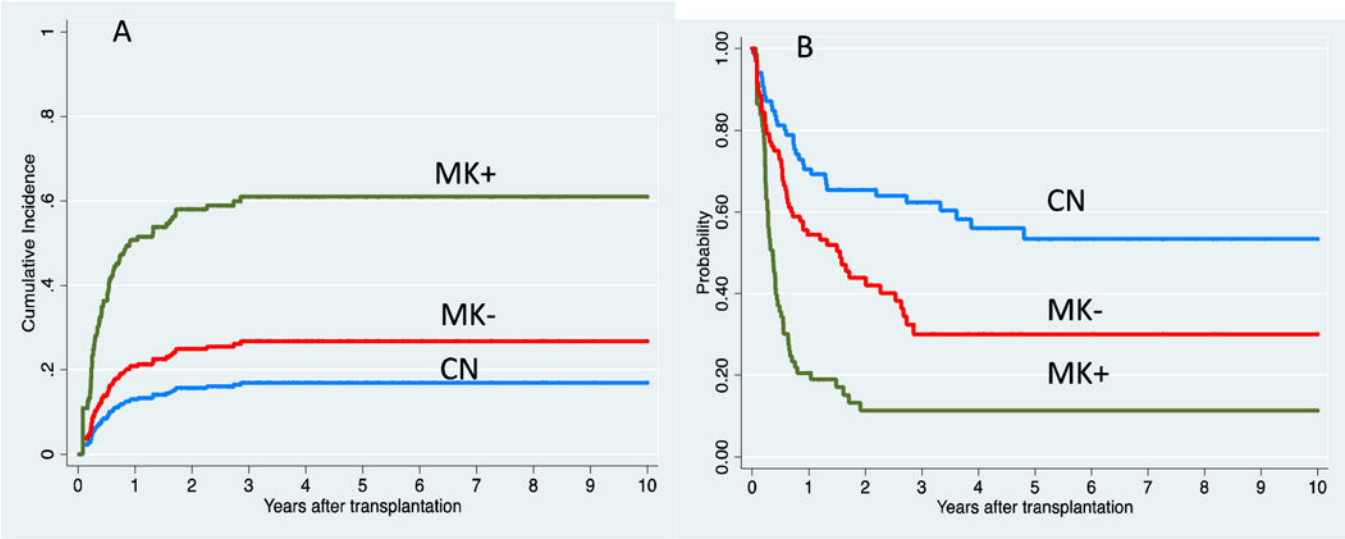

Figure 1: Cumulative relapse incidence (A) and event-free survival (B) after hematopoietic stem cell transplantation by monosomal karyotype in MDS patients.

Cytogenetic classification with monosomal karyotype (MK) was able to identify three difference risk groups for MDS patients who had allogeneic hematopoietic stem cell transplantation. (A) MK+ patients comprised a very high-risk group with 3-year RI of 60.9% in contrast to good risk normal cytogenetics (CN) patients with 3-year RI of 16.9%. MK− patients comprised an intermediate-risk group with 3-year RI of 26.7%, (B) EFS was similar; MK+ , MK− and CN patients had 3-year EFS of 11.4%, 30% and 62.3% respectively.

Table 1:

Patient and disease characteristic by MDS therapy prior to HSCT

Variable	Whole cohort		Untreated		Chemo only		HMA only		Chemo+HMA		
	n	%	N=78	%	N=40	%	N=122	%	N=16	%	P
Age	256										
Median		56	52		55		59		59		
IQR		48–62	45–57		44–60		53–64		56–60		0.0001
WHO histological subtype											
Low/Intermediate	74	28.9	27	34.6	7	17.5	38	31.2	2	12.5	
High risk	100	39.1	13	16.7	26	65.0	51	41.8	10	62.5	
CMML	23	9.0	3	3.8	4	10.0	12	9.8	4	25.0	
MDS-U	59	23.0	35	44.9	3	7.5	21	17.2	0		<0.001
Therapy related MDS	92/256	35.9	43	55.1	12	30.0	37	30.3	0		<0.001
Cytogenetics by 5 group risk	254/256										
Very Good/Good	105	41.3	27	35.1	19	47.5	52	43.0	7	43.7	
Intermediate	32	12.6	9	11.7	6	15.0	13	10.7	4	25.0	
Poor	46	18.1	22	28.4	5	12.5	18	14.9	1	6.3	
Very Poor	71	28.0	19	24.7	10	25.0	38	31.4	4	25.0	0.2
MK	254/256										
CN	102	40.2	27	35.1	17	42.5	51	42.1	7	43.8	
MK−	79	31.1	30	39.0	14	35.0	29	24.0	6	37.5	
MK+	73	28.7	20	25.9	9	22.5	41	33.9	3	18.7	0.3
IPSS-R at diagnosis	144/256										
Very Low/Low	40	27.8	11	32.4	2	8.4	23	31.1	4	33.3	
Intermediate	18	12.5	6	21.8	5	20.8	5	6.8	2	16.7	
High	22	15.3	6	20.5	6	25.0	9	12.2	1	8.3	
Very High	37	25.7	2	14.1	6	25.0	25	33.8	4	33.3	
Missing	27	18.8	9	16.7	5	20.8	12	16.2	1	8.3	0.03
Morphological response by IWR *	178/256										
Complete remission	46	25.8			12	30.0	31	25.4	3	18.8	
Active disease	132	74.2			28	70.0	91	74.6	13	81.2	0.7

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Variable	Whole cohort		Untreated		Chemo only		HMA only		Chemo+HMA		
Persistent karyotype abnormality at HSCT**	106/113										
No	35	33.0			9	37.5	24	33.3	2	20	
Yes	71	67.0			15	62.5	48	66.7	8	80	0.6
BM blast at HSCT, %											
<5	169	66.0	55	70.5	25	62.5	79	64.8	10	62.5	
≥5	87	34.0	23	29.5	15	37.5	43	35.2	6	37.5	0.8
Ferritin level	201/256		47/78		21/40		118/122		15/16		
Median	1131		1077		1555		997		1748		
IQR	521–2246		389–2637		1100–2503		425–2010		1002–3211		0.03
Stem cell source											
PB	169	66.0	56	71.8	22	55.0	78	63.9	13	81.3	
BM	87	34.0	22	28.2	18	45.0	44	36.1	3	18.7	0.2
Donor source											
Matched related	133	52.0	54	69.2	19	47.5	52	42.6	8	50.0	
Matched unrelated	123	48.0	24	30.8	21	52.5	70	57.4	8	50.0	0.003
Conditioning regimen											
MAC	162	63.3	55	70.5	24	60.0	72	59.0	11	68.8	
RIC	94	36.7	23	29.5	16	40.0	50	41.0	5	31.2	0.4
Time to HSCT from diagnosis											
Median	8		5.5		6.9		9.0		12.7		
IQR	5.2–15.3		3.4–12.5		5.5–12.3		6.0–16.8		6.8–32.9		0.0001
Transplant year											
Before 2005	62	24.2	36	46.1	26	65	0		0		
After 2005	194	75.8	42	53.9	14	35	122	100	16	100	<0.001
Median follow up of survivors (mo)											
Median	33.9		38.4		88.3		26.6		25.9		
IQR	17–63.4		18.1–73.4		51.6–125.1		15.5–45		16.6–58.5		0.01

*Only patients that received MDS therapy prior to HSCT were included.

**Only patients with abnormal cytogenetics and had cytogenetic evaluation at HSCT were included.

Abbreviations: IQR, interquartile range; HR, hazard ration, CI, confidence interval; OS, overall survival; WHO, World Health Organization; CMML, chronic myelomonocytic leukemia; MDS-U, myelodysplastic syndrome unclassifiable; MK, monosomal karyotype; CN, normal cytogenetics; IPSS-R, International prognostic scoring system-revised; HSCT, hematopoietic stem cell transplantation; BM, bone marrow ANC, absolute neutrophil count; PB, peripheral blood; CB, cord blood; MRD, matched related donor; MUD, matched unrelated donor; RIC, reduced intensity conditioning; MAC, myeloablative conditioning.

Table 2:

Univariate results for RI, TRM, EFS and OS

	RI		TRM		EFS		OS	
Variable	HR	p	HR	p	HR	p	HR	P
Age per 10 years	1.06	0.5	1.4	0.002	1.3	0.002	1.3	0.002
WHO histological subtype								
Low/Intermediate	Ref		Ref		Ref		Ref	
High risk	2.0	0.02	1.0	0.9	1.6	0.02	1.5	0.05
CMML	1.5	0.3	1.4	0.4	1.6	0.1	1.5	0.2
MDS-U	1.0	0.9	1.4	0.2	1.3	0.2	1.3	0.2
Therapy related MDS	1.4	0.1	1.2	0.4	1.5	0.02	1.5	0.01
Cytogenetics by 5 group risk								
Very Good/Good	Ref		Ref		Ref		Ref	
Intermediate	1.2	0.7	1.4	0.4	1.4	0.2	1.3	0.3
Poor	1.4	0.4	1.2	0.5	1.4	0.2	1.6	0.06
Very Poor	3.9	<0.0001	1.1	0.6	3.4	<0.0001	3.3	<0.0001
MK								
CN	Ref		Ref		Ref		Ref	
MK−	1.2	0.5	1.4	0.2	1.5	0.06	1.6	0.03
MK+	4.1	<0.0001	1.2	0.5	3.7	<0.0001	3.7	<0.0001
Previous therapy for MDS								
Untreated	Ref		Ref		Ref		Ref	
Chemo only	1.1	0.7	1.5	0.3	1.4	0.2	1.4	0.2
HMA only	1.0	0.9	1.5	0.1	1.3	0.2	1.4	0.1
Chemo+HMA	0.8	0.7	1.8	0.2	1.2	0.5	1.5	0.3
Response by IWG at HSCT								
Complete remission	Ref		Ref		Ref		Ref	
Advanced disease	0.8	0.3	1.7	0.1	1.1	0.5	1.3	0.2
Untreated	0.8	0.5	1.0	0.9	0.8	0.5	0.9	0.6
Cytogenetic remission**								
Yes	Ref		Ref		Ref		Ref	

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	RI		TRM		EFS		OS	
No	1.2	0.6	1.0	0.9	1.3	0.2	1.5	0.1
BM blast at HSCT								
<5%	ref		Ref		Ref		Ref	
≥5%	2.0	0.01	0.9	0.8	1.6	0.006	1.6	0.006
Ferritin level								
≤1130	Ref		Ref		Ref		Ref	
>1130	1.0	0.8	2.0	0.009	1.6	0.01	2.0	0.001
Missing	1.7	0.06	1.2	0.6	1.5	0.05	1.7	0.02
Stem cell source								
PB	Ref		Ref		Ref		Ref	
BM	0.9	0.9	1.4	0.2	1.2	0.3	1.3	0.1
Donor source								
Matched related	ref		Ref		ref		Ref	
Matched unrelated	0.7	0.2	1.7	0.02	1.2	0.3	1.4	0.06
Conditioning regimen								
MAC	Ref		Ref		ref			
RIC	0.6	0.05	2.1	0.001	1.2	0.2	1.2	0.4
Time to transplantation after diagnosis, months								
≤8mo	Ref		Ref		ref			
>8 mo	0.6	0.03	1.2	0.5	0.8	0.1	0.8	0.1
Transplant year								
Before 2005	Ref		Ref		Ref		Ref	
After 2005	0.8	0.3	0.8	0.4	0.7	0.1	0.7	0.1

Abbreviations: RI, relapse incidence; TRM, transplant related mortality; EFS, event-free survival; OS, overall survival; HR, hazard ratio; WHO, World Health Organization; CMML, chronic myelomonocytic leukemia; MDS-U, myelodysplastic syndrome unclassifiable; IPSS, International prognostic scoring system; MK, monosomal karyotype; CN, normal cytogenetics; IPSS-R, International prognostic scoring system-revised; HMA, hypomethylating agents; IWG, International Working Group; HSCT, hematopoietic stem cell transplantation; BM, bone marrow ANC, absolute neutrophil count; PB, peripheral blood; RIC, reduced intensity conditioning; MAC, myeloablative conditioning.

Table 3:

Multivariate analyses for RI, TRM, EFS and OS

	RI*		TRM**		EFS^		OS^^	
Variable	HR	p	HR	p	HR	p	HR	p
Age per 10 years								
			1.3	0.04	1.4	<0.001	1.4	<0.001
WHO histological subtype	NS							
Low/intermediate risk					1.0		1.0	
High risk					1.8	0.007	1.7	0.01
CMML					2.3	0.009	2.3	0.01
MDS-U					1.6	0.08	1.6	0.09
MK								
CN	1.0				1.0		1.0	
MK−	1.3	0.4			1.9	0.005	1.7	0.02
MK+	4.2	<0.0001			5.2	<0.001	4.9	<0.0001
Ferritin level								
≤1150			1.0		1.0		1.0	
>1150			1.7	0.06	1.8	0.002	2.2	<0.001
Missing			0.7	0.4	1.0	0.9	1.1	0.2
BM blast at HSCT							NS	
<5%	1.0				1.0		1.0	
≥5%	1.6	0.01			1.2	0.3	1.3	0.2
Donor								
Matched related			1.0				1.0	
Matched unrelated			1.8	0.02			1.6	0.01
Transplant year								
Before 2005			1.0		1.0		1.0	
After 2005			0.4	0.006	0.4	0.002	0.4	0.001

*RI is adjusted for histological subtype, MK, bone marrow blast count at HSCT, conditioning intensity and time to HSCT.

**TRM is adjusted for age, serum ferritin level at HSCT, donor type, conditioning intensity and transplant year.

^ EFS is adjusted for age, histological subtype, t-MDS, MK, serum ferritin, bone marrow blast count at HSCT and transplant year.

^^ OS is adjusted for age, histological subtype, t-MDS, MK, serum ferritin and bone marrow blast count at HSCT, donor type and transplant year.

Abbreviations: OS, overall survival; EFS, event free survival; HR, hazard ratio; CI, confidence interval; range; CMML, chronic myelomonocytic leukemia; MDS-U, myelodysplastic syndrome unclassifiable; MK, monosomal karyotype; CN, normal cytogenetics; NS, not significant