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Monosomal karyotype at the time of diagnosis or transplantation predicts outcomes of Allogeneic Hematopoietic Cell Transplantation in Myelodysplastic Syndrome

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Abstract

Various cytogenetic risk scoring systems may determine prognosis for patients with myelodysplastic syndromes (MDS). We evaluated four different risk scoring systems in predicting outcome after allogeneic hematopoietic cell transplantation (alloHCT). We classified 124 patients with MDS using the International prognostic scoring system (IPSS), the revised international prognostic scoring system (R-IPSS), Armand's transplantation-specific cytogenetic grouping (TSCG), and monosomal karyotype (MK) both at the time of diagnosis and alloHCT. After adjusting for other important factors, MK at diagnosis (compared to no MK) was associated with poor 3-year disease-free survival (DFS) (27% (95% CI, 12-42%) versus 39% (95% CI, 28-50%), p=0.02) and overall survival (OS) (29% (95% CI, 14-44%) versus 47% (95% CI, 36-59%), p=0.02). OS but not DFS was affected by MK at HCT. MK frequency was uncommon in low score R-IPPS and IPSS. Although IPSS and R-IPSS discriminated good/very good groups from poor/very poor groups, patients with intermediate risk scores had the worst outcomes and therefore these scores did not show a progressive linear discriminating trend. Cytogenetic risk score change between diagnosis and alloHCT was uncommon and did not influence OS. MK cytogenetics in MDS are associated with poor survival suggesting the need for alternative or intensified approaches to their treatment.

Keywords

Myelodysplastic syndrome; allogeneic hematopoietic cell transplantation; relapse; monosomal karyotype; cytogenetics; cytogenetic scoring systems

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Introduction

Myelodysplastic syndromes (MDS) are heterogeneous diseases characterized by bone marrow dysplasia, cytopenias, and frequent evolution to acute myelogenous leukemia.[1] Several scoring systems, including the International Prognostic Scoring System (IPSS), utilize clinical and molecular features, including cytogenetics, to risk-stratify patients.[2] The IPSS was recently revised (R-IPSS).[3] This revision maintained bone marrow cytogenetics, marrow blast percentage, and cytopenias as the basis of the new system, with increased stratification within these categories. Cytogenetics has been a major component of all MDS scoring systems. The R-IPSS defines five cytogenetic subgroups: very good, good, intermediate, poor, and very poor [3, 4] whereas the IPSS only includes three cytogenetic patterns: good, intermediate, and poor.[2] These scoring systems are used prognostically and to aid clinical decision-making at initial presentation [5, 6]. Higher risk patients are often recommended for hematopoietic cell transplantation (alloHCT), the only potentially curative treatment for MDS [7-11]. The IPSS and R-IPSS scoring systems have been shown to predict alloHCT outcomes.[12-15] In addition to these scoring systems, Armand et al created and verified transplant-specific cytogenetic grouping (TSCG) (standard risk vs. adverse risk) that influenced the outcomes of alloHCT [16, 17]. Other cytogenetic groupings recognizing the monosomal karyotype (MK) are also found to impact on OS in MDS patients.[18, 19] The molecular/genetic prognostic landscape remains complex in MDS, and it is not clear which prognostic system, the IPSS, R-IPSS, TSCG, or presence/absence of MK, are the most clinically relevant in the setting of alloHCT.

To address this question, we compared the ability of these four cytogenetic risk stratification systems to predict alloHCT outcomes. Since some MDS patients referred for alloHCT may have evolution in their cytogenetic risk scores during pre-transplant therapy, we also evaluated the frequency of change within each cytogenetic risk score from diagnosis to alloHCT and whether these changes had any impact on alloHCT outcomes.

Patients and Methods

Patient Populations

Through the University of Minnesota Blood and Marrow Transplant (BMT) database, we identified adult MDS patients (≥ 18 years) who underwent their first alloHCT between 1995 and 2012. One hundred and twenty-four patients who had ≤10% myeloblasts in the bone marrow at the time of alloHCT (only 9 patients had >10% blasts at alloHCT) and had cytogenetic data at both diagnosis and alloHCT were included in the analysis. (By excluding patients with high blast counts at alloHCT, we were able to focus on the effect of the cytogenetic scoring systems on outcomes. Our prior analysis showed that high blast counts had a marked effect on outcome [20], making it difficult to control for the higher level blasts when evaluating the impact of cytogenetic scoring, particularly in a cohort of relatively limited number of patients.) Umbilical cord blood (UCB) and volunteer unrelated donors (URDs) were considered when there was no HLA-matched sibling available. Depending on the urgency of transplant or availability of study protocols UCB was at times prioritized over URD. UCB were selected using criteria that we have previously published [21, 22]. UCB grafts were matched at 4–6 of 6 HLA-A, -B (Ag level) and -DRB1 (allele level) to the

recipient, and in patients receiving two UCB units, to each other.[23, 24] In addition to the HLA matching, stem cell count in UCB unit was considered in donor selection.

Definitions

MK was defined as the presence of any autosomal monosomy accompanied by either one additional autosomal monosomy or one structural chromosomal abnormality.[25] Cytogenetic classifications of IPSS, R-IPSS, and TSCG were described per published studies,[2-4] and are summarized in a supplemental table (Table 2). Relapse was defined as any recurrence of known hematologic, morphologic, or cytogenetic markers consistent with disease prior to transplant. GVHD data was captured prospectively by attending physicians at regular post-HCT intervals and graded using standard criteria with histopathologic confirmation when possible. [26-29] Graft source and matching was defined as matched (HLA 8/8 allele matched) versus mismatched (HLA <8/8 matched) bone marrow/peripheral blood stem cell (BM/PBSC) and matched (HLA 5/6 locus or 6/6 antigen matched) versus mismatched (HLA <5/6) umbilical cord blood (UCB).[23, 24] Conditioning regimen intensity was defined according to Bacigalupo et al.[30] Patients receiving acute myelogenous leukemia (AML)-type induction regimens or hypomethylating agents were defined as chemotherapy group.

Disease-Related Variables

Diagnostic specimens were reviewed by hematopathologists at our institution and classified according to the current 2008 World Health Organization (WHO) MDS criteria.[31] Therapy-related MDS (t-MDS) was clinically defined as MDS following exposure to alkylating agents, topoisomerase II inhibitors, or radiotherapy within an appropriate timeframe. Clinical variables, histopathologic data, cytogenetic information and data on therapy were obtained via retrospective chart review. Two authors (B.T., M.D.) independently scored all available diagnostic and transplant cytogenetics; discrepancies were resolved after consensus review. Standard G-banding and FISH techniques were used for cytogenetic analysis, with at least 20 metaphase cells analyzed by G-banding and 200 interphase cells analyzed by FISH.

Conditioning Regimens

Conditioning regimens have been previously reported for myeloablative (MAC)/reduced intensity conditioning (RIC) related or URD sources and MA/RIC UCB donor sources. [32-34] Per institutional protocol, equine anti-thymocyte globulin (ATG) (15 mg/kg twice daily × 3 days) was provided to patients who had not received multi-agent chemotherapy within 3 months of HCT when using a UCB or URD or 6 months when using a matched-related donor (MRD).

Supportive Care

All patients received supportive care according to institutional guidelines including blood product transfusion, infection prophylaxis (bacterial, fungal, cytomegalovirus (CMV)/herpes simplex virus (HSV) and Pneumocystis jiroveci), and GVHD prophylaxis. CMV surveillance was performed weekly with pre-emptive treatment at the time of positive

antigenemia or polymerase chain reaction (PCR) testing. For GVHD prophylaxis, the majority of patients received cyclosporine (CSA)-based regimens (targeting trough levels of 200-400 ng/mL) through day +180 with either short course methotrexate (MTX) in MA regimens or mycophenolate mofetil (MMF) through day +30 with RIC or UCB regimens. Granulocyte-colony stimulating factor was administered to all patients through neutrophil recovery. Chimerism was determined by quantitative PCR of informative polymorphic variable number tandem repeat or short tandem repeat regions in the recipient and donor as described.[23]

Data Collection and Analysis

Patient outcomes following alloHCT were prospectively collected and recorded in the University of Minnesota BMT database. Treatment protocols were approved by the University of Minnesota Institutional Review Board and registered at http://clinicaltrials.gov, and all patients gave informed consent before alloHCT. Factors considered in statistical analysis included the following: patient age, sex, Karnofsky performance status (KPS), recipient CMV serostatus, year of transplant, donor graft source, conditioning regimen intensity, GVHD prophylactic regimen, MDS diagnosis according to WHO criteria [35], available cytogenetics, t-MDS, all four cytogenetic risk scoring systems at both diagnosis and alloHCT, and blast percentage at diagnosis and transplant.

Statistical Methods

Unadjusted estimates of OS and DFS were calculated by Kaplan-Meier curves.[36] Comparisons were completed with the simple log rank test. Unadjusted estimates of non-relapse mortality (NRM) were analyzed using cumulative incidence treating relapse as a competing risk. Relapse was similarly analyzed using cumulative incidence treating mortality as a competing risk. Comparisons were completed with Gray's test. Cox regression was used to assess the independent effect of cytogenetic indices on OS and DFS.[37] and Fine and Gray proportional hazards regression [38]was used to assess the independent effect of indices on NRM and relapse. Martingale residuals were used to test against non-proportionality.[39] with tests for linear contrasts. After calculation of final regression models, the adjusted OS and DFS curves by MK were computed as average estimates of the pooled sample, weighted by the proportions of the variables in the regression models.[40] Similarly, the adjusted relapse and NRM curves by MK were estimated based on other significant risk factors in the regression models. [41] SAS 9.3 (SAS Institute, Cary, NC) and R 3.0.2 were used to perform all statistical analyses.

Results

Patients' demographic data are shown in Table 1. The median age was 55 years, and the majority of patients (62%) received alloHCT after RIC. Twenty-three percent of patients had t-MDS. Patients were grouped by four cytogenetic scoring systems at the time of diagnosis and at alloHCT (Table 2). Changes in the cytogenetic score between diagnosis and alloHCT occurred in 22%, 22%, 14%, and 10% of patients in the IPSS, R-IPSS, TSCG, and MK cytogenetic scoring systems, respectively (Table 2).

Patients with or without MK had no significant difference in patient-, disease-, or transplantation- related characteristics except for more therapy-related MDS in MK patients (Table 3). The frequency of receiving chemotherapy before alloHCT was also similar in these groups. IPSS cytogenetic risk score groups had similar characteristics except the poor risk group had a lower blast percentage, more MK, and more patients with therapy-related MDS (Table 3). MK was most common in very poor R-IPSS risk (28/29, 96%) followed by poor (6/30, 20%), intermediate (1/24, 4%), good (1/34, 2.9%), and very good cytogenetic risk groups (0/2, 0%). R-IPSS very poor group had also more patients with therapy-related MDS.

The adjusted Kaplan-Meier estimates of OS and DFS and cumulative incidence estimates of relapse and NRM by cytogenetic scoring system groupings are shown in Table 4. Similarly, multiple regression analysis, showing the relative risk of patients with MK as well as other confounding factors, is shown in Table 5. Patients with MK at diagnosis had lower survival (Figure 1 A and B) and higher relapse. Relapse/progression was the cause of mortality in 52% and 20% of patients with MK and without MK at diagnosis, respectively. In a different model, when MK at alloHCT was evaluated, it was associated with decreased OS (HR, 1.9; CI95%:1.1-3.3, p=0.03) but not relapse (HR, 1.7; CI95%:0.8-3.9, p=0.17). Patients with IPSS good cytogenetic risk score (either at diagnosis or alloHCT) had the best DFS, OS, and relapse rates whereas intermediate risk group had the highest relapse rate and the shortest survival. Similarly, patients with R-IPSS very good/good cytogenetic risk score (either at diagnosis or alloHCT) had the longest DFS and OS whereas intermediate risk group had the worst survival. Neither R-IPSS nor IPSS predicted outcomes in an expected linear fashion ($p > 0.05$) due to poor outcomes in the intermediate group. Outcomes by TSCG were similar between the adverse or favorable groups. In the regression analyses that focused on the effect of patients with and without MK, other risk factors for poor OS and higher relapse were MM RD/URD and RIC without ATG in multivariate regression analysis, respectively (Table 5). UCBT had no significant effect on relapse, TRM, DFS or OS in MVA.

Changes in cytogenetic risk score between diagnosis and alloHCT appeared to have no impact on NRM or OS, regardless of scoring system. All three patients progressing to unfavorable risk from standard risk score by TSCG died (two after relapse). Prior chemotherapy had no effect on relapse, DFS or OS in univariate analysis.

Discussion

The Importance of MK in predicting MDS prognosis continues to emerge. Non-transplant studies have shown that MK has more a significant effect on survival compared with that found in other classification systems for complex cytogenetics in MDS.[18, 42, 43] The few recent studies evaluating the importance of MK in alloHCT have reported results similar to ours. In a specific cohort of MDS patients with chromosome 7 abnormalities, Van Gelder et al, using the European Group for Blood and Marrow transplantation (EBMT) database, showed that MK was more predictive of progression-free survival and OS after alloHCT than complex cytogenetics in 261 MDS or AML patients.[19] In fact, MK and marrow blast counts of >5% were the only prognostic factors for DFS in MDS patients receiving alloHCT.[44] Deeg et al reported that both MK and R-IPSS cytogenetic risk score were

associated with relapse and survival after alloHCT in MDS patients.[15] In our study, MK was more predictive of alloHCT outcomes in MDS patients after alloHCT compared to other established scoring systems. Moreover, the presence of MK, both at diagnosis and at alloHCT, was predictive of survival after alloHCT; to our knowledge, ours is the first study to evaluate this. We also showed that MK frequency was correlated with R-IPSS cytogenetic risk score; the highest frequency of MK was found in the R-IPSS very poor cytogenetic risk group and was progressively less frequent in the more favorable risk groups, similar to the findings of Deeg et al.[15] Although some studies indicate that a complex karyotype is more prognostic than MK in the non-alloHCT MDS setting, [45, 46] we could not evaluate this because of the strong correlation between MK and R-IPSS very poor cytogenetic risk group (>3 cytogenetic abnormalities).

The IPSS and R-IPSS have been shown in previous studies to be associated with outcomes of alloHCT [12, 15, 47, 48]. Our study as in line with other studies in that it highlights the predictive potential of IPSS and R-IPSS primarily in the good risk cytogenetic groups that had the best expected outcomes after alloHCT. In addition, we noted a worsening trend for relapse, DFS and OS from the good/very good risk group toward the poor/ very poor risk group. However, the intermediate risk groups classified by both IPSS and R-IPSS had unexpectedly poor outcomes (the highest NRM and relapse yielding the lowest DFS and OS) in our cohort. When we compared factors among risk scoring groups in IPSS and R-IPSS scoring system such as blast percentage or inferior KPS, there was no significant difference to explain the poor outcome in the intermediate groups. In our study we found that the TSCG had no utility in predicting alloHCT outcomes.[16, 17] The difference between our study and other large studies [15, 48] may be due in part to the limited number of patients in our study. Moreover, our study cohort had the largest UCBT. UCBT has been used in MDS patients.[20, 49, 50] Although there is no study directly comparing UCBT with other graft sources for MDS, comparable results were shown in acute myelogenous leukemia.[51, 52] In our study, UCBT frequency was similar within the cytogenetic scoring systems, and was not found to be associated with relapse, TRM, DFS or OS.

Changes between diagnosis and alloHCT in cytogenetics risk score group in each scoring system occurred were uncommon. These cytogenetic changes had little influence on outcomes of alloHCT. In general, the value of cytogenetic risk scoring in alloHCT outcomes was similar between classification at diagnosis and at alloHCT. Although this was not one of the primary objectives of our retrospective analysis and the patient cohort was relatively small, this might indicate that outcomes of alloHCT were not affected significantly by therapy between diagnosis and alloHCT. The effect of therapy in MDS before alloHCT is still controversial, mainly due to reported all results are from retrospective studies.[7, 48, 53-57] In a large single center study, Oran et al showed that therapy prior to alloHCT and disease status at alloHCT were not found to be prognostic for any disease outcome.[44] OS at 5 years was 57% for patients who underwent alloHCT as a primary treatment for RAEB-t or secondary AML and 54% for those who underwent alloHCT in remission after induction chemotherapy (p=0.81).[53] In that study, achieving a CR before a standard alloHCT was not to be associated with a better prognosis posttransplantation; however, disease status had a significant impact in patients who progressed to AML. In contrast, other studies have indicated CR status is important for alloHCT outcomes.[47, 57-59] In our prior study, we

highlighted the importance of blast percentage at the time of transplant in MDS patients [20]. Consequently, to focus this analysis on the impact of cytogenetic risk group instead of confounding characteristic of high blast burden, we excluded a limited number of patients who had >10% marrow blasts at alloHCT in this cohort. A recent EBMT study showed that in patients with high risk cytogenetic score by IPSS, relapse rate at 5-year was much higher if they were in CR (70%) versus not in CR (38%). However, relapse was lower in patients with low risk cytogenetic score in CR (38% vs. 18%). [48] These findings in others and our study may suggest that cytogenetic risk group may be more important than CR status in MDS- CR is a difficult end point to measure in MDS, regardless.

In conclusion, this study evaluates the ability of 4 different cytogenetic scoring systems used at diagnosis and alloHCT to predict outcome. We found that MK, particularly at diagnosis, is the cytogenetic risk scoring system most predictive of post alloHCT outcomes. Changes in the cytogenetics risk score between diagnosis and alloHCT occur only rarely and have limited effects on outcomes of alloHCT. Therefore, cytogenetic risk scoring at diagnosis or at alloHCT seemed to have similar power of prediction of alloHCT outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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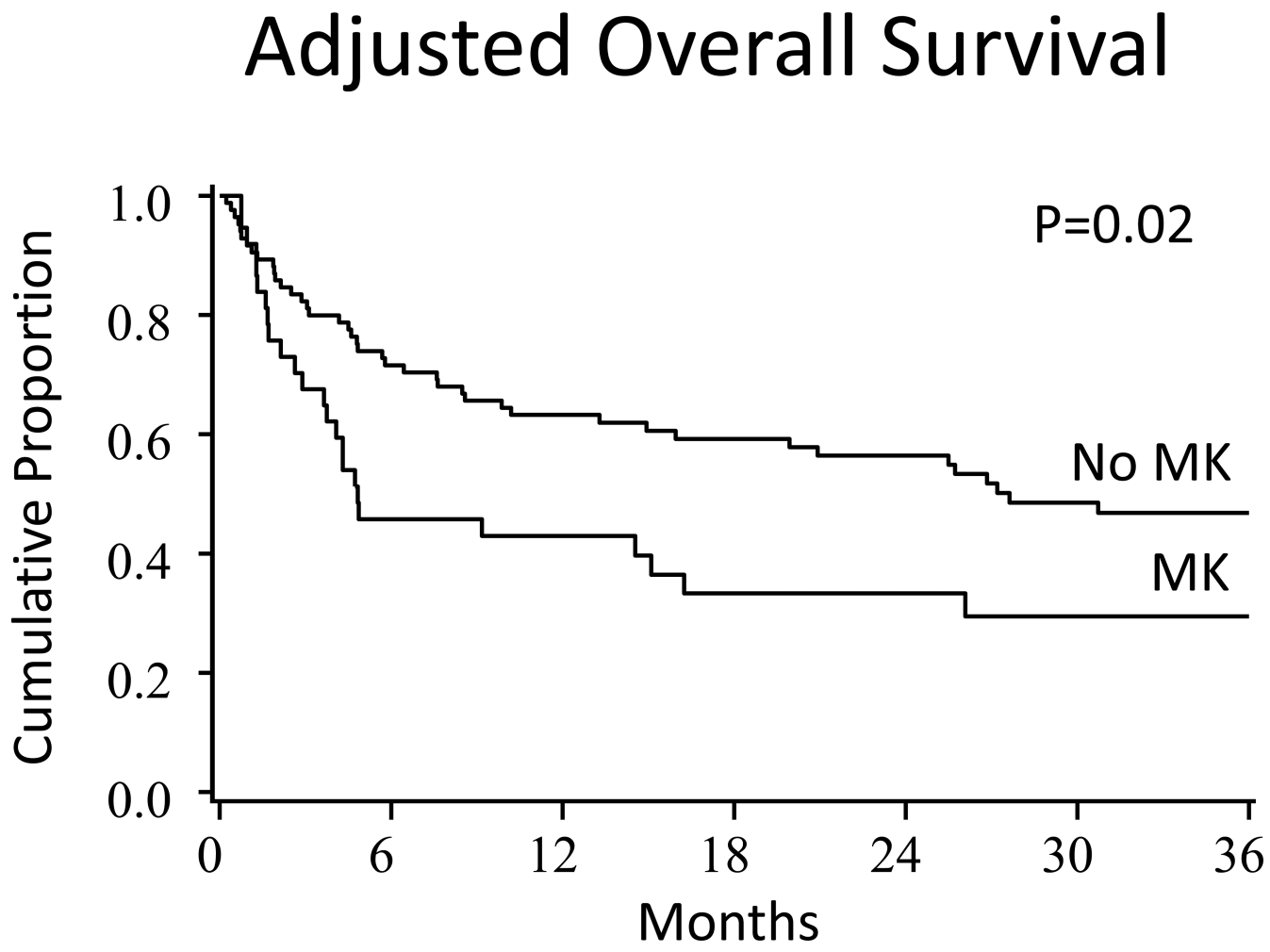

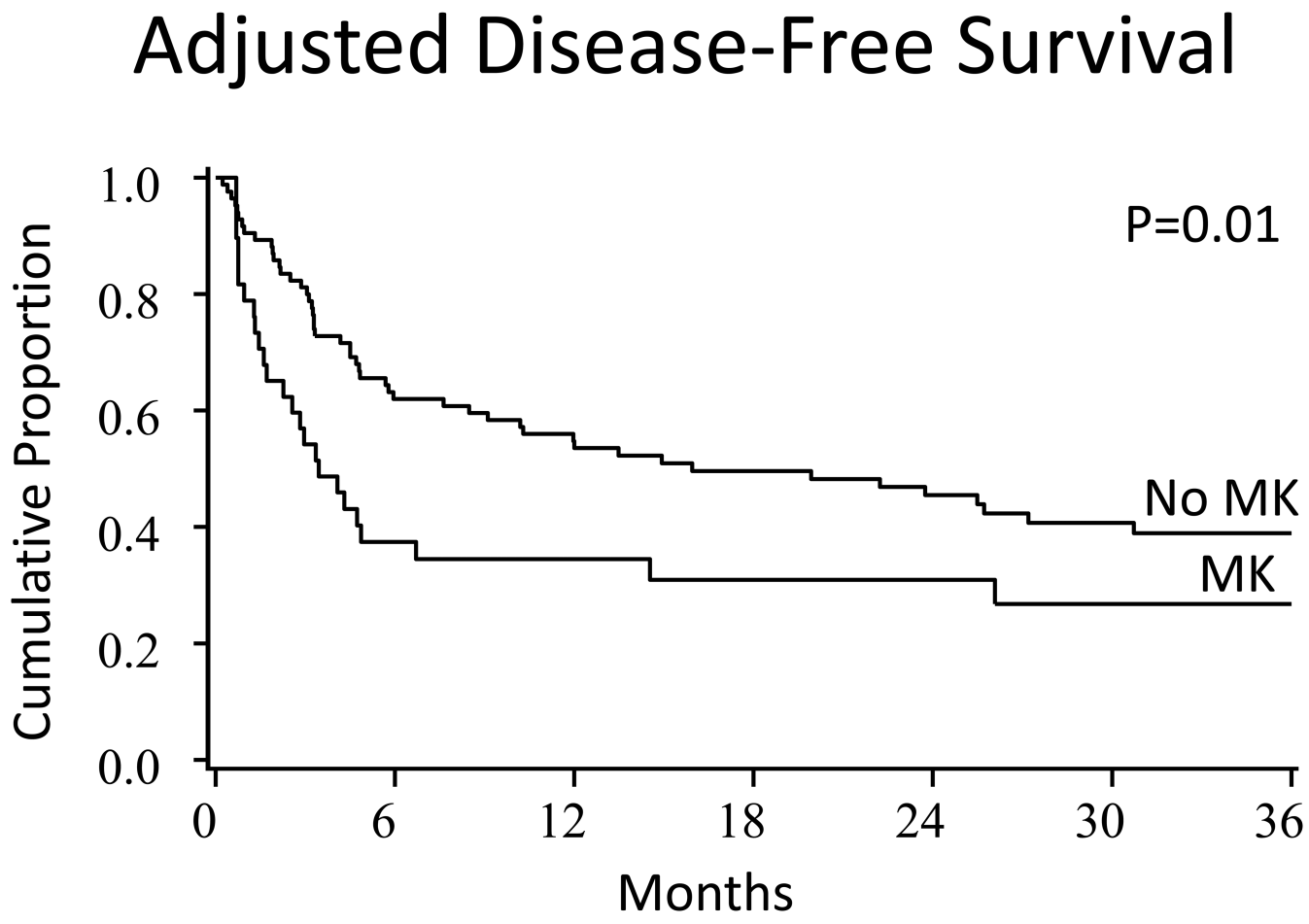

Figure 1. OS (A) and DFS (B) at 3 years by MK

Table 1
Patient- and Transplantation-Characteristics

Variable		Total Study Group
Year of Transplant	1995-1999	16 (13%)
	2000-2006	40 (32%)
	2007-2013	68 (55%)
Age of Patients	< 50	41 (33%)
	50-60	47 (38%)
	>60	36 (29%)
Median (range) (IQR)		55 (18-72), (47-62)
Patient Gender	Male	83 (67%)
KPS	<90	25 (21%)
	90/100	97 (80%)
Recipient CMV Serostatus	Negative	57 (46%)
	Positive	67 (54%)
Donor Type	RD/URD Match	67 (54%)
	RD/URD MM	8 (7%)
	UCB 5+6/6	24 (19%)
	UCB 4/6	25 (20%)
Conditioning	MAC	47 (38%)
	RIC: w/ ATG	52 (42%)
	RIC: w/o ATG	25 (20%)
GvHD Prophylaxis	CSA/MMF	75 (61%)
	CSA containing	31 (25%)
	Other	18 (15%)
Diagnosis	MDS-NOS	24 (19%)
	MDS - RA	5 (4%)
	MDS - RAEB-1	34 (27%)
	MDS - RAEB-2	30 (24%)
	MDS - RARS	4 (3%)
	MDS - RCMD	21 (17%)
	RCMD - RS	6 (5%)
Months from Diagnosis to Transplant:	Median (range), (IQR)	6 (1-371), (4-13)
Therapy-related MDS	No	94 (77%)
	Yes	28 (23%)
Blast at alloHCT	<=2%	74 (60%)
	>2-<5%	33 (27%)
	5-10%	17 (14%)

Abbreviations: AlloHCT, allogeneic hematopoietic cell transplantation; CMV, cytomegalovirus; CSA, cyclosporine; GVHD, graft-versus-host disease; IPSS, International Prognostic Scoring System; R-IPSS, International Prognostic Scoring System-revised; KPS, Karnofsky performance status; MAC, myeloablative conditioning; MDS, myelodysplastic syndrome; MDS-U, MDS- unclassifiable; MRD, matched related donor; MMRD, mismatched related donor; MTX, methotrexate; RIC, reduced intensity conditioning; MMF, mycophenolate mofetil; MDS, myelodysplastic syndrome; NOS, not otherwise specified; RA, refractory anemia; RAEB, refractory anemia with excess blasts; RARS, refractory anemia with

ringed sideroblasts; RD, related donor; RCMD, refractory cytopenias with multilineage dysplasia; RCMD/RS, RCMD with ringed sideroblasts; UCB, umbilical cord blood; URD, unrelated donor; WHO, World Health Organization

Table 2

Cytogenetic risk scores by various systems at diagnosis and alloHCT

Scoring System	Cytogenetics Risk Score	At Diagnosis	At AlloHCT	Change in cytogenetic score between Diagnosis and AlloHCT	
IPSS	Good	35 (29%)	44 (37%)	Improved	17 (15%)
	Intermediate	28 (23%)	26 (22%)	No change	91 (78%)
	Poor	58 (48%)	50 (42%)	Progression	9 (8%)
R-IPSS	Very good	2 (2%)	1 (1%)	Improved	16 (14%)
	Good	34 (28%)	44 (37%)	No change	91 (78%)
	Intermediate	24 (20%)	24 (20%)	Progression	10 (9%)
	Poor	32 (26%)	25 (21%)		
	Very poor	29 (24%)	25 (21%)		
TSCS	Favorable	63 (52%)	71 (59%)	Improved	13 (11%)
	Adverse	59 (48%)	49 (41%)	No change	102 (86%)
				Progression	3 (3%)
MK	No	83 (70%)	90 (75%)	Improved	9 (8%)
	Yes	36 (30%)	30 (25%)	No change	104 (90%)
				Progression	3 (3%)

Abbreviations: AlloHCT, allogeneic hematopoietic cell transplantation; IPSS, International Prognostic Scoring System; R-IPSS, International Prognostic Scoring System-revised; MK, monosomal karyotype; TSCG transplant-specific cytogenetic grouping.

Table 3

Patient Characteristics by Monosomal Karyotype and IPSS at Diagnosis

					IPSS				R-IPSS				
Variable		**No MK**	**MK**	**P-value**	**Good**	**Intermediate**	**Poor**	**P-value**	**Good/ Very Good**	**Intermediate**	**Poor**	**Very Poor**	**P-value**
Age of Patient	< 50	26 (31%)	13 (36%)	0.82	6 (17%)	14 (50%)	20 (35%)	0.03	6 (17%)	11 (46%)	15 (47%)	8 (28%)	**0.04**
	50-60	32 (39%)	14 (39%)		13 (37%)	8 (29%)	25 (43%)		13 (36%)	8 (33%)	11 (34%)	14 (48%)	
	>60	25 (30%)	9 (25%)		16 (46%)	6 (21%)	13 (22%)		17 (47%)	5 (21%)	6 (19%)	7 (24%)	
Age (Years)	Median (range)	55 (19-72)	52 (19-69)	0.88	58 (27-72)	52 (21-69)	52 (19-72)	0.11	59 (27-72)	53 (28-69)	51 (19-72)	53 (22-69)	0.17
Patient Gender	Male	55 (66%)	24 (67%)	0.97	23 (66%)	17 (61%)	40 (69%)	0.75	23 (64%)	16 (67%)	23 (72%)	18 (62%)	0.86
KPS	<90	19 (23%)	5 (14%)	0.29	6 (17%)	7 (25%)	11 (19%)	0.73	7 (19%)	6 (25%)	7 (22%)	4 (14%)	0.80
	90/100	64 (77%)	30 (83%)		29 (83%)	21 (75%)	46 (79%)		29 (81%)	18 (75%)	25 (78%)	24 (86%)	
Recipient CMV	Positive	46 (55%)	19 (53%)		19 (54%)	18 (64%)	28 (48%)	0.38	20 (56%)	16 (67%)	14 (44%)	15 (52%)	0.39
Donor Type	RD/URD Match	42 (51%)	23 (64%)	0.44	17 (49%)	14 (50%)	35 (60%)	0.19	18 (50%)	12 (50%)	16 (50%)	20 (69%)	0.22
	RD/URD MM	6 (7%)	2 (6%)		2 (6%)	4 (14%)	2 (3%)		2 (6%)	4 (17%)	1 (3%)	1 (3%)	
	UCB 5+6/6	19 (23%)	4 (11%)		11 (31%)	3 (11%)	10 (17%)		11 (31%)	3 (13%)	6 (19%)	4 (14%)	
	UCB 4/6	16 (19%)	7 (19%)		5 (14%)	7 (25%)	11 (19%)		5 (14%)	5 (21%)	9 (28%)	4 (14%)	
Conditioning	MA	32 (39%)	13 (36%)	0.97	11 (31%)	11 (39%)	24 (41%)	0.78	11 (31%)	8 (33%)	16 (50%)	11 (38%)	0.61
	RIC: w/ ATG	35 (42%)	16 (44%)		17 (49%)	10 (36%)	24 (41%)		18 (50%)	9 (38%)	11 (34%)	13 (45%)	
	RIC: w/o ATG	16 (19%)	7 (19%)		7 (20%)	7 (25%)	10 (17%)		7 (19%)	7 (29%)	5 (16%)	5 (17%)	
GvHD Prophylaxis	CSA/MMF	52 (63%)	21 (58%)	0.57	23 (66%)	18 (64%)	32 (55%)	0.77	24 (67%)	17 (71%)	17 (53%)	15 (52%)	0.49
	CSA containing	21 (25%)	8 (22%)		8 (23%)	7 (25%)	15 (26%)		8 (22%)	4 (17%)	11 (34%)	7 (24%)	
	Other	10 (12%)	7 (19%)		4 (11%)	3 (11%)	11 (19%)		4 (11%)	3 (13%)	4 (13%)	7 (24%)	
Diagnosis	MDS-NOS	12 (15%)	10 (28%)	0.30	6 (17%)	5 (18%)	13 (22%)	**0.04**	6 (17%)	5 (21%)	13 (21%)	5 (17%)	0.05
	MDS - RA	5 (6%)	0		1 (3%)	2 (7%)	2 (3%)		1 (3%)	3 (13%)	1 (3%)	0	
	MDS - RAEB-1	21 (25%)	11 (31%)		7 (20%)	6 (21%)	19 (33%)		18 (50%)	4 (17%)	2 (6%)	6 (21%)	
	MDS - RAEB-2	25 (30%)	5 (14%)		18 (51%)	5 (18%)	7 (12%)		2 (6%)	0	1 (3%)	1(3%)	
	MDS - RARS	3 (4%)	1 (3%)		1 (3%)	1 (4%)	2 (3%)		1 (3%)	5 (21%)	7 (22%)	8 (28%)	
	MDS - RCMD	13 (16%)	8 (22%)		1 (3%)	7 (25%)	13 (22%)		1 (3%)	2 (8%)	1 (3%)	1 (3%)	
	RCMD - RS	4 (5%)	1 (3%)		1 (3%)	2 (7%)	2 (3%)		7 (19%)	5 (21%)	12 (38%)	8 (28%)	

					IPSS				R-IPSS				
Variable		**No MK**	**MK**	**P-value**	**Good**	**Intermediate**	**Poor**	**P-value**	**Good/ Very Good**	**Intermediate**	**Poor**	**Very Poor**	**P-value**
Therapy-related MDS	yes	13 (16%)	13 (36%)	**0.01**	16 (46%)	5 (18%)	6 (10%)	**<0.01**	1 (3%)	4 (17%)	13 (41%)	19 (68%)	**<0.01**
Blast at TX	<=2%	46 (55%)	27 (75%)	0.07	21 (60%)	15 (54%)	38 (66%)	**0.53**	22 (61%)	13 (54%)	18 (56%)	21 (72%)	0.61
	>2-<5%	25 (30%)	4 (11%)		11 (31%)	8 (29%)	11 (19%)		11 (31%)	7 (29%)	8 (25%)	4 (14%)	
	5-10%	12 (15%)	5 (14%)		3 (9%)	5 (18%)	9 (16%)		3 (8%)	4 (17%)	6 (19%)	4 (14%)	
Chemotherapy	No	43 (52%)	16 (44%)	0.46	34 (97%)	23 (85%)	35 (61%)	<0.01	35 (97%)	23 (96%)	24 (80%)	1 (3%)	**<0.01**
	Yes	40 (48%)	20 (56%)		1 (3%)	4 (15%)	22 (39%)		1 (3%)	1 (4%)	6 (20%)	28 (97%)	
MK	No				34 (97%)	27 (96%)	22 (39%)	<0.01	6.7 (1-372)	7.4 (2-63)	5.4 (2-73)	5.2 (2-38)	0.06
	Yes				1 (3%)	1 (4%)	34 (61%)		1 (3%)	4 (17%)	13 (41%)	19 (68%)	**<0.01**
Months to AlloHCT	Median (range)	6.7 (1-372)	5.3 (2-39)	0.14	6.3 (1-77)	10.4 (2-81)	5.3 (2-372)	0.58	22 (61%)	13 (54%)	18 (56%)	21 (72%)	0.61

Table 4

The effects of cytogenetic scoring system groupings on alloHCT outcomes adjusted for donor type, conditioning and baseline Karnofsky

Time	Cytogenetic scoring systems	Cytogenetic Risk Score	NRM at 3 years	P-value	Relapse at 3 years	P-value	DFS at 3 years	P-value	OS at 3 years	P-value
AT DIAGNOSIS	**IPSS**	Good	22%(8-36%)	0.01	21%(8-34%)	0.28	59%(43-73%)	<0.01	67%(51-83%)	<0.01
		Intermediate	55%(45-65%)		35%(17-53%)		11%(1-23%)		16%(4-30%)	
		Poor	42%(28-56%)		26%(15-37%)		32%(20-44%)		37%(24-50%)	
	R-IPSS	Very Good/Good	21%(7-35%)	<0.01	23%(9-37%)	0.02	57%(41-73%)	<0.01	66%(50-82%)	<0.01
		Intermediate	59%(38-80%)		36%(17-55%)		8%(1-19%)		19%(3-35%)	
		Poor	47%(29-65%)		10%(1-21%)		41%(24-58%)		44%(26-62%)	
		Very Poor	35%(16-54%)		39%(22-56%)		24%(7-41%)		27%(11-44%)	
	TSCG	Standard	36%(24-48%)	0.29	28%(17-39%)	0.98	37%(25-49%)	0.36	44%(31-57%)	0.28
		Adverse	44%(31-57%)		26%(15-37%)		31%(19-43%)		36%(24-48%)	
	MK	No	40%(29-51%)	0.96	23%(14-32%)	0.02	39%(28-50%)	0.01	47%(36-59%)	0.02
		Yes	35%(19-51%)		38%(23-43%)		27%(12-42%)		29%(14-44%)	
AT ALLOHCT	**IPSS**	Good	27%(13-41%)	0.19	27%(14-40%)	0.86	47%(32-62%)	0.09	57%(42-72%)	<0.01
		Intermediate	56%(36-76%)		29%(12-46%)		19%(4-34%)		22%(6-38%)	
		Poor	43%(29-57%)		25%(13-37%)		32%(19-45%)		36%(22-50%)	
	R-IPSS	Very Good/Good	27%(13-31%)	0.23	29%(16-52%)	0.84	45%(30-60%)	0.02	56%(41-71%)	<0.01
		Intermediate	59%(39-79%)		27%(10-44%)		18%(3-33%)		24%(6-42%)	
		Poor	37%(17-57%)		18%(2-34%)		44%(23-65%)		49%(29-69%)	
		Very Poor	46%(26-66%)		31%(14-47%)		24%(6-42%)		23%(6-40%)	
	TSCG	Standard	40%(28-52%)	0.51	27%(17-37%)	0.73	36%(24-48%)	0.27	42%(31-54%)53%)	0.34
		Adverse	41%(27-54%)		28%(16-40%)		32%(19-45%)		38%(24-52%)	
	MK	No	41%(31-51%)	0.85	25%(16-34%)	0.17	36%(26-46%)	0.10	43%(33-53%)	0.08
		Yes	39%(21-60%)		34%(18-50%)		28%(12-44%)		31%(14-48%)	

Table 5

Multiple regression analyses through 3 years for NRM, Relapse, DFS and OS

Factors*	N	RR of NRM (95% CI)	P-value	RR of Relapse (95% CI)	P-value	RR of Relapse/Death (95% CI)	P-value	RR of Death (95% CI)	P-value
MK at Diagnosis									
No	83	1.0		1.0		1.0		1.0	
Yes	36	1.0 (0.5-2.0)	0.96	**2.4 (1.1-5.3)**	**0.02**	**2.0 (1.2-3.4)**	**0.01**	**1.9 (1.1-3.3)**	**0.02**
Donor Type									
Matched RD/URD	67	1.0		1.0		1.0		1.0	
MM RD/URD	8	**5.9 (2.4-14.5)**	**<0.01**	**No events**	**<0.01**	**2.8 (1.2-6.4)**	**0.02**	**3.7 (1.6-8.8)**	**<0.01**
5+6/6 UCB	24	0.9 (0.4-2.4)	0.91	0.5 (0.2-1.5)	0.26	0.7 (0.4-1.5)	0.40	0.7 (0.3-1.6)	0.45
4/6 UCB	25	1.2 (0.5-2.6)	0.88	0.9 (0.4-2.3)	0.85	1.0 (0.5-1.8)	0.96	1.2 (0.6-2.3)	0.58
Conditioning									
MAC	47	1.0		1.0		1.0		1.0	
RIC: w/ ATG	52	1.1 (0.5-2.4)	0.87	2.1 (0.8-5.5)	0.13	1.6 (0.9-2.8)	0.14	1.5 (0.8-2.8)	0.20
RIC: w/o ATG	25	1.3 (0.6-2.9)	0.48	**3.4 (1.3-9.3)**	**0.02**	**2.3 (1.2-4.4)**	**0.01**	**2.2 (1.1-4.2)**	**0.02**
KPS									
90-100*	97	1.0		1.0		1.0		1.0	
<90	25	1.1 (0.6-2.2)	0.73	1.5 (0.6-4.0)	0.43	1.7 (1.0-3.0)	0.06	1.6 (0.9-3.0)	0.10
Grade II-IV AGVHD (Time Dependent)									
No	76	1.0		1.0		1.0		1.0	
Yes	48	1.0 (0.5-2.0)	0.99	0.7 (0.3-1.5)	0.33	0.7 (0.4-1.1)	0.12	0.9 (0.5-1.6)	0.78

* Tested for MK at Diagnosis (No versus Yes), Age (<50 versus 50-60 versus 60+), year of alloHCT (1995-1999 versus 2000-2006 versus 2007-2013), gender (male versus female), KPS (<90 versus 90/100), cmv serostatus (positive versus negative), donor type (RD/URD match versus RD/URD MM versus 5+6/6 UCB versus 4/6 UCB), conditioning (Myeloablative versus RIC with ATG versus RIC w/o ATG), GvHD prophylaxis (cyclosporine/mycophenolate mofetil versus cyclosporine/other versus other), diagnosis (RA/RARS versus RAEB versus RCMD versus unknown), treatment related MDS (No versus Yes) and Blasts at alloHCT (≤2% versus 3-4% versus 5-10%).