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Hematopoietic Cell Transplantation Outcomes in Monosomal Karyotype Myeloid Malignancies

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Abstract

The presence of monosomal karyotype (MK+) in acute myeloid leukemia (AML) is associated with dismal outcomes. We evaluated the impact of MK+ in AML (MK+AML, N=240) and in myelodysplastic syndrome (MK+MDS, N=221) on hematopoietic cell transplantation (HCT) outcomes compared to other cytogenetically defined groups (AML, N=3,360; MDS, N=1,373) as reported to the Center for International Blood and Marrow Transplant Research (CIBMTR) from 1998 to 2011. MK+AML was associated with higher disease relapse (hazard ratio [HR] 1.98, p<0.01), similar transplant related mortality (TRM, HR 1.01, p=0.9) and worse survival (HR 1.67, p<0.01) compared to other cytogenetically defined AML. Among patients with MDS, MK+MDS was associated with higher disease relapse (HR 2.39, p<0.01), higher TRM (HR 1.80, p<0.01) and worse survival (HR 2.02, p<0.01). Subset analyses comparing chromosome 7 abnormalities

(del7/7q) with or without MK+ demonstrated higher mortality for MK+ disease in for both AML (HR 1.72, p<0.01) and MDS (HR1.79, p<0.01). The strong negative impact of MK+ in myeloid malignancies was observed in all age groups and using either myeloablative or reduced intensity conditioning regimens. Alternative approaches to mitigate disease relapse in this population are needed.

Introduction

The presence of multiple chromosomal abnormalities, termed complex cytogenetics, in leukemia cells, is associated with unfavorable outcome. The reported definitions of complex cytogenetics varies from ≥3 to 5 cytogenetic abnormalities in a single clone(1, 2). Breems et al further examined this group of patients with poor risk disease and identified autosomal monosomies to be associated with poor outcome(3). This classification has a tighter association with poor outcome comparing to other non-random cytogenetic changes in the poor risk category and predicts a subset of patients with dismal outcome. The monosomal karyotype (MK) is defined as the presence of at least two autosomal monosomies or one autosomal monosomy associated with any other structure abnormality (MK+). Cytogenetic abnormalities have similar prognostic impact in myelodysplastic syndrome (MDS) where the number of chromosomal abnormalities is also associated with poor outcomes (4, 5) and in MDS, MK+ is strongly associated with shorter survival, similar to acute myeloid leukemia (AML) (6). In both AML and MDS, abnormalities in chromosome 7 including deletion and monosomy, are common single abnoermality associated with poor prognosis. The prognostic effect of MK+ could be due to single most common monosomy.

Hematopoietic cell transplantation (HCT) is the treatment of choice for patients with cytogenetic-defined poor risk AML in first complete remission (CR1), which may lead to 30 to 40% 5 year survival compared to <10% with non-transplant approaches(1, 7, 8). However, these data are mostly from patients younger than 60 years receiving allogeneic transplantation with myeloablative (MA) conditioning. Reduced intensity conditioning (RIC) is commonly used in AML patients older than 60 years (9). This reduction in intensity decreases toxicity and early transplant mortality allowing older or compromised patients to receive an allogeneic HCT. However, when comparing with MA approaches, this benefit is offset by increase in relapse rates(10). Additionally, a retrospective analysis done by the European Group for Blood and Marrow Transplantation (EBMT) demonstrated that poor risk cytogenetics at diagnosis is associated with higher relapse and shorter leukemia-free survival (LFS) in patients with AML in CR1 receiving RIC compared to myeloablative conditioning (11).

Older AML patients more often have increased cytogenetic abnormalities including unfavorable risk and MK(3, 12, 13). MK+ AML may increase the risk of relapse after transplantation(14–18) however it is unclear whether MA conditioning may mitigate this increased relapse risk. We analyzed the effect of MK+ AML in patients undergoing HCT in CR1 and explored the prognostic impact of the MK+ in transplants for MDS.

Materials and Methods

Data Sources

The Center for International Blood and Marrow Transplant Research (CIBMTR) includes a voluntary working group of more than 450 transplantation centers worldwide that contribute detailed data on consecutive allogeneic and autologous hematopoietic cell transplantation to a statistical center at the Medical College of Wisconsin in Milwaukee and the National Marrow Donor Program (NMDP) Coordinating Center in Minneapolis. Participating centers are required to report all transplants consecutively; patients are followed longitudinally and compliance is monitored by on-site audits. Computerized checks for discrepancies, physicians' review of submitted data and on-site audits of participating centers ensure data quality. Observational studies conducted by the CIBMTR are performed in compliance with all applicable federal regulations pertaining to the protection of human research participants. Protected Health Information used in the performance of such research is collected and maintained in CIBMTR's capacity as a Public Health Authority under the HIPAA Privacy Rule(9).

Patients

All patients with AML in CR1 who received a first allogeneic HCT from 1998 to 2011 from HLA-matched or single HLA locus mismatched donors (8/8 or 7/8) were eligible for this study.

Patients with acute promyelocytic leukemia or evidence of t(15;17) as a sole cytogenetic abnormality, core binding factor AML, who received umbilical cord blood grafts, ex-vivo T-cell depleted grafts or patients with unknown cytogenetic information were excluded.

MK+AML was defined as the presence of two monosomies or one monosomy plus at least one other chromosome structural abnormality according to Breems et al(3). Cytogenetic abnormalities present at diagnosis and prior to initiation of conditioning regimen are reported to the CIBMTR. When required, additional review of reported cytogenetic data was performed by three reviewers (MCP, BCM and MB) to adjudicate any uncertainties in classification. Cases with incomplete data were classified as unknown cytogenetics and excluded.

Eligible AML patients were categorized into MK+ AML (N=240), AML other unfavorable (N=1138) and intermediate risk groups (2). The intermediate risk was further separated into normal karyotype (N=643) and intermediate risk with abnormal karyotype (AML-IR^{abn}, N=1579). Eligible MDS patients were categorized into MK+MDS (N=221), MDS other unfavorable (N=423), normal karyotype (N=241), MDS- IR^{abn} (N=611) and favorable karyotype (N=98)(4). MDS cases were also classified as early and advanced according to the CIBMTR definition(9). Subset analysis to compare abnormalities of chromosome 7 (monosomy or deletion) with or without meeting the MK+ definition was performed separately in AML and MDS divided as: MK+ with chromosome 7 abnormalities (MK/7abn, AML N=148, MDS N=171), chromosome 7 without MK+ (7abn, AML n=275, MDS n=304) and normal karyotype (AML N=643, MDS=241).

Study Endpoints and Variables

The cytogenetic groups were compared for the clinical endpoints of overall survival, disease-free survival (DFS), relapse and transplant related mortality (TRM). Overall survival included time from HCT until death from any cause and patients were censored at last follow up. DFS included death, leukemia or MDS relapse as a composite endpoint and patients were censored at last follow up. Relapse included any reported events of leukemia relapse. TRM was defined as death in the absence of prior leukemia [or MDS] relapse.

Variables analyzed in the multivariate model include: cytogenetic groups, age, performance score, conditioning regimen intensity(19), donor type, donor/recipient CMV serologic status, graft source, year of transplant, graft versus host disease (GVHD) prophylaxis, use of in vivo T-cell depletion (anti-thymocyte globulin [ATG] or alemtuzumab), planned use of any myeloid growth factor to promote engraftment (defined as any growth factor initiated within 12 days after the graft infusion). Conditioning intensity use was confounded by the age of the patient with RIC mostly utilized in patients older than 40 years. For the analysis age and conditioning intensity were combined into composite covariate groups as: 1) myeloablative (MA) < 21years, MA 21–40 years, MA 41–60 years, RIC 41–60 years, RIC 61–64 years, RIC ≥65 years.

Statistical Analysis

Probabilities of overall survival and DFS were calculated using the Kaplan-Meier estimator. Values for relapse and TRM were generated using cumulative incidence estimates adjusting for competing risks.

The cytogenetic groups were compared using proportional hazards regression models for overall mortality (1- overall survival), relapse and TRM. The proportional hazards assumptions for all the variables were examined by adding a time-dependent covariate as necessary. Time dependent covariates with piecewise constant of regression coefficients were used to model time-varying effect when the proportionality assumption did not hold with the optimal time cut point determined by the maximum likelihood method. The proportionality assumption was further examined for the piecewise constant regression coefficient Cox model. A forward stepwise method was used to build the regression model for the outcomes of relapse, TRM and overall mortality. Since the cytogenetic groups were the main interest of this study, this variable was included in all steps of model building procedure with other covariates retained as indicated. Risk factors with significance level of $p < 0.05$ were included in the model. The potential interaction between main effect of cytogenetic group and all significant covariates was examined. For the subset analysis focus on chromosome 7 abnormalities, the same models were built with the main effect modified. Adjusted probabilities of LFS and OS were computed based on final Cox regression model, stratified by status groups, and weighted by the pooled sample proportion value for all significant risk factors. These adjusted probabilities estimate likelihood of outcomes in populations with similar prognostic factors. SAS version 9.2 was used in all analyses.

Results

Demographics

Tables 1a and b outline the demographics of patients with AML and MDS cohorts, respectively. Patients with MK+ AML were generally older than IR^{abn} and other unfavorable cohorts, but similar to patients with normal karyotype. Leukocyte count at diagnosis was lower for MK+AML than the other groups. The proportion of patients with extra medullary disease or therapy-related AML was similar across the groups. There were a higher proportion of patients with <90% KPS and recipients of RIC regimens in the MK+ AML cohort. Additionally, peripheral blood stem cells (PBSC) was the predominant graft source for patients with MK+ AML and normal karyotype. The time from diagnosis to transplant, year of transplant, GVHD prophylaxis, use of growth factor support and in vivo T-cell depletion were similar across the AML cytogenetic groups. Among patients with MDS, MK+MDS and patients with normal karyotype were older than the other groups. The MK+MDS group had more patients with performance score less than 90%, and both MK +MDS and MDS- IR^{abn} had a higher proportion of patients with pre-HCT marrow blasts between 11–20%. High International Prognostic Staging System (IPSS) was mainly observed in patients with MK+MDS and other unfavorable groups due to the cytogenetic component of the score. Patients with MK+MDS had a shorter time from diagnosis to transplant than others. Greater than 70% of patients in both unfavorable cytogenetic groups had evidence of abnormalities of chromosome 7. Similar to AML, most patients with MDS received PBSC as the graft source. Other variables including year of transplant, conditioning regimen intensity, GVHD prophylaxis, use of growth factor support and in vivo T-cell depletion were similar across the MDS groups.

Disease Relapse

Three-year cumulative incidences of leukemia relapse were 52% (95% confidence interval [CI], 42–58%), 36 % (95% CI, 34–39%), 25% (95% CI, 23–27%) and 30 (95% CI, 26–34%) for MK+ AML, other unfavorable, IR^{abn} and normal karyotype, respectively ($p<0.001$) (Figure 1a). Multivariate analysis of leukemia relapse demonstrated that MK+AML was associated with higher relapses compared to normal karyotype (relative risk [RR] 1.98, 95% CI 1.58–2.49, $p<0.001$) (Table 2), to IR^{abn} (RR 2.20, 95% CI 1.78–2.72, $p<0.001$) and to other unfavorable (RR 1.46, 95% CI 1.19–1.79, $p<0.001$). AML with other unfavorable cytogenetics was associated with higher relapse risk compared to normal karyotype (RR 1.36, 95% CI 1.14–1.63, $p<0.001$) and to IR^{abn} (RR 1.51, 95% CI 1.32–1.74, $p<0.001$). Other variables associated with higher rates of leukemia relapse include older age and reduced conditioning intensity, lower performance score and graft source (Appendix, Table A). Older patients receiving RIC experienced higher disease relapses compared to younger patients receiving MA conditioning. Among patients age 41–60 years, those who received a MA regimen had lower relapse risks than recipients of RIC (RR 0.58 95% CI, 0.49–0.69, $p<0.001$). Additionally recipients of PBSC experienced lower rates of relapse compared to bone marrow recipients (RR 0.84 95% CI, 0.73–0.98, $p=0.02$). For MDS patients, the 3-year cumulative incidence of relapse were 44% (95% CI, 37–51%), 32% (95% CI, 27–36%), 26% (95% CI, 23–30%), 28% (95% CI, 22–34%) and 29% (95% CI, 20–39%) for MK+ AML, other unfavorable, IR^{abn}, normal karyotype and favorable groups, respectively

(p<0.001) (Figure 1b). Multivariate analysis of MDS relapse demonstrated that MK+MDS was associated with higher relapses compared to normal karyotype (RR 2.39, 95% CI 1.74–3.29, p<0.001)(Table 2), to IR^{abn} (RR 2.13, 95% CI 1.64–2.76, p<0.001), to other unfavorable (RR 1.59, 95% CI 1.21–2.09, p<0.001) and to favorable (RR 2.01 95% CI, 1.32–3.06, p=001). Other variables associated with higher rates of MDS relapse include older age/RIC, lower performance score, BM grafts, ATG or Alemtuzumab, no planned use of growth factor and advanced disease status at transplant (Appendix Table B). Younger patients and recipients of MA experienced lower relapse rates. Among patients age 41–60 years MA conditioning led to lower relapse risks than RIC/NMA (RR 0.67 95% CI, 0.51–0.90, p=0.007). The planned use of growth factor was associated with lower relapse rates in MDS (RR 0.79 95% CI, 0.66–0.95, p=0.01).

Transplant Related Mortality

For AML, the 3-year cumulative incidences of TRM were 22% (95% CI, 17–27%), 22 % (95% CI, 19–24%), 20% (95% CI, 18–22%) and 20 (95% CI, 17–23%) for MK+ AML, other unfavorable, IR^{abn} and normal karyotype, respectively (p=0.75). Multivariate analysis showed no impact of cytogenetic abnormalities on TRM for AML (p=0.41). Other variables associated with TRM were age/conditioning intensity, lower performance score, conditioning regimen type, unrelated and HLA mismatched donor, PBSC grafts, GVHD prophylaxis, planned use of growth factors and year of transplant (Appendix Table C).

For MDS the 3-year cumulative incidences of TRM were 37% (95% CI, 30–44%), 32% (95% CI, 27–37%), 27% (95% CI, 24–31%), 26% (95% CI, 20–32%) and 28 (95% CI, 19–38%) for MK+ MDS, other unfavorable, IR^{abn}, normal karyotype and favorable, respectively (p=0.07). Multivariate analysis of TRM in MDS showed that MK+MDS was associated with higher TRM compared to normal karyotype (RR 1.80, 95% CI 1.27–2.54, p<0.001)(Table 2), to IR^{abn} (RR 1.79, 95% CI 1.34–2.38, p<0.001), to other unfavorable (RR 1.31, 95% CI 0.98–1.76, p=0.07) and to favorable (RR 1.89 95% CI, 1.22–2.94, p=0.005). Other variables associated with higher rates of TRM in MDS include older age/conditioning intensity, lower performance score, unrelated 7/8 HLA matched donor, advanced disease status and year of transplant (Appendix Table D).

Graft-versus-Host Disease

Cumulative incidences of grades II–IV acute GVHD at day 100 among patients with AML were 43% (95% CI, 37–49%), 35% (95% CI, 32–38%), 30% (95% CI, 28–32%) and 33% (95% CI, 30–37%) for MK+ AML, other unfavorable, IR^{abn} and normal karyotype, respectively (p<0.01). Cumulative incidences of chronic GVHD at 1 year among patients with AML were 44% (95% CI, 37–50%), 43% (95% CI, 40–46%), 44% (95% CI, 42–47%) and 48% (95% CI, 44–52%) for MK+ AML, other unfavorable, IR^{abn} and normal karyotype, respectively (p=0.26).

Cumulative incidences of grades II–IV acute GVHD at day 100 among patients with MDS were 48% (95% CI, 41–54%), 45% (95% CI, 40–50%), 39% (95% CI, 35–42%), 38% (95% CI, 31–44%) and 42 (95% CI, 32–51%) for MK+ MDS, other unfavorable, IR^{abn}, normal karyotype and favorable, respectively (p=0.03). Cumulative incidences of chronic GVHD at

1 year among patients with MDS were 39% (95% CI, 33–46%), 25% (95% CI, 21–29%), 23% (95% CI, 19–26%), 22% (95% CI, 17–28%) and 25% (95% CI, 17–34%) for MK+ MDS, other unfavorable, IR^{abn}, normal karyotype and favorable, respectively (p=0.03).

Disease Free Survival and Overall Survival

Three-year probabilities of DFS in AML were 27% (95% CI, 21–33%), 42% (95% CI, 39–45%), 55% (95% CI, 52–58%) and 50 (46–54%) for MK+ AML, other unfavorable, IR^{abn} and normal karyotype, respectively (p<0.001). Corresponding three-year probabilities for overall survival in AML were 29% (95% CI, 24–35%), 46% (95% CI, 43–49%), 58% (95% CI, 56–61%) and 55 (51–59%), respectively (p<0.001) (Figure 1c). Multivariate analysis of overall mortality demonstrated that MK+AML was associated with higher mortality compared to normal karyotype (RR 1.67, 95% CI 1.38–2.01, p<0.001) (Table 2), to IR^{abn} (RR 1.84, 95% CI 1.55–2.19, p<0.001) and to other unfavorable (RR 1.37, 95% CI 1.15–1.62, p<0.001). AML with other unfavorable was associated with higher mortality compared to normal karyotype (RR 1.22, 95% CI 1.06–1.40, p<0.001) and to IR^{abn} (RR 1.35, 95% CI 1.20–1.50, p<0.001). Other variables associated with higher rates of leukemia relapse include older age/conditioning intensity, lower performance score, unrelated or HLA mismatched donor and year of transplant (Appendix Table E). Older patients receiving RIC were associated with higher mortality compared to younger patients receiving myeloablative conditioning. Among patients age 41–60 years a MA regimen led to lower mortality than RIC (RR 0.77 95% CI, 0.67–0.89, p<0.001).

Three-year probabilities of DFS in MDS were 19% (95% CI, 13–25%), 36% (95% CI, 32–41%), 46% (95% CI, 42–50%), 46% (95% CI, 40–53%) and 42% (95% CI, 32–53%) for MK+ MDS, other unfavorable, IR^{abn}, normal karyotype and favorable, respectively (p<0.01). Corresponding three-year probabilities for overall survival in MDS were 22% (95% CI, 16–29%), 42% (95% CI, 37–47%), 53% (95% CI, 49–57%), 52% (95% CI, 45–59%) and 48% (95% CI, 38–59%) for MK+ MDS, other unfavorable, IR^{abn}, normal karyotype and favorable, respectively (p<0.01) (Figure 1d). Multivariate analysis of overall mortality demonstrated that MK+MDS was associated with higher mortality compared to normal karyotype (RR 2.02, 95% CI 1.59–2.59, p<0.001)(Table 2), to IR^{abn} (RR 2.11, 95% CI 1.73–2.58, p<0.001), to other unfavorable (RR 1.45, 95% CI 1.19–1.78, p<0.001) and to favorable (RR 2.02 95% CI, 1.22–2.78, p=001). MDS with other unfavorable was associated with higher mortality compared to normal karyotype (RR 1.39, 95% CI 1.10–1.77, p=0.006), to IR^{abn} (RR 1.45, 95% CI 1.22–1.72, p<0.001) and to favorable (RR 1.39, 95% CI 1.03–1.88, p=0.03). Other variables associated with higher mortality in MDS include older age/conditioning intensity, lower performance score, unrelated 7/8 HLA matched donor, advanced disease status and year of transplant (Appendix Table F). Younger patients and recipients of MA experienced better survival. Among patients age 41–60, MA conditioning led to similar survival as RIC (RR 0.95 95% CI, 0.79–1.15, p=0.62).

Chromosome 7 Abnormalities Subset Analyses

For this subset, both the AML and MDS cohorts were stratified into three groups: MK+ with abnormal −7/−7q (MK+/abn7, AML N=148, MDS N=171), abnormal −7/−7q without MK (AML N=275, MDS N=304) and normal karyotype (AML N=643, MDS N=241). The

demographic differences across these groups were similar to those in the whole population for AML and MDS. Among patients with AML, there was higher relapse and worse survival for patients with MK+/7Abn (Figure 2a). Multivariate analysis confirmed a higher mortality with MK+/7abn compared to normal karyotype (RR 1.98 95% CI, 1.58–2.46, p<0.001) and abn7 without MK+ (RR 1.72 95% CI, 1.34–2.20, p<0.001). Among patients with MDS, patients with MK+/7abn experienced higher TRM, more relapse and worse survival (Figure 2b). Multivariate analysis among patients with MDS confirmed higher mortality with MK+/7abn compared to normal karyotype (RR 2.06 95% CI, 1.58–2.68, p<0.001) and abn7 without MK+ (RR 1.79 95% CI, 1.39–2.32, p<0.001).

Discussion

This large analysis of patients with MK+ AML in CR1 and MDS who received an allogeneic HCT confirms the finding of higher risks of relapse and significantly worse post-HCT outcomes compared to other cytogenetically defined groups including other previously defined unfavorable groups. The worse survival in MK+AML was mainly driven by excess in relapse, whereas in MK+MDS led to excess risks of both TRM and relapse. We also explored the conditioning regimen effect within the cytogenetically defined groups. Generally, younger patients who received a MA regimen had better outcomes in AML. Among patients within 40–61 years, MA resulted in better survival than RIC for AML but not in MDS (Appendix Tables). However, the adverse prognostic impact of MK+ disease was not overcome by conditioning intensity and we observed no significant interactions between these two variables.

The incidence of MK+AML is reported in 11 to 13% of patients with AML and approximately 30% in patients with AML with abnormal cytogenetics (3, 12, 13, 20). MK+ AML patients are generally older age, with low leukocyte count at diagnosis and more often have complex cytogenetics as observed in this study. Medeiros et al analyzed a large series from patients with AML enrolled in upfront clinical trials in the US and reported a 20% incidence of MK+AML in patients older than 60 years. Kayser et al in a series of 319 patients with MK+ AML from the German-Austrian AML Study Group also observed MK+ patients to be older with lower leukocyte count at diagnosis and associated with abnormalities of chromosomes 7, 5, 17p, 18q, 20q, 3 and complex karyotype (20). Interestingly, patients with MK+AML present less frequently with commonly observed molecular markers such as FLT3 internal tandem duplication, NMP-1 mutation and tyrosine kinase domain mutations (20).

MK+ is closely related to complex cytogenetics, and as initially defined by Breems et al, MK+ represents a subset of the unfavorable risk with exceptionally poor outcomes(3). Complex cytogenetics is a general definition with a number of cytogenetic abnormalities, 3–5 or greater(2). The prognosis with MK+ is worse than complex cytogenetics, likely related the higher proportion of TP53 deletion seen in MK+AML (20–23). However, patients with many cytogenetic abnormalities most often also meet the criteria for MK+. Thus for MK+ there is general loss of chromosomes and complex cytogenetics without MK+ includes a hyperdiploid karyotype. Additionally, most poor risk single karyotypic abnormalities in AML include loss of chromosome 5/5q, 7/7q, 12p, 17p, 18/18q and 20 which are correlated

with MK+ (12, 24–27). Phenotypic analysis of leukemic blasts demonstrated that co-expression of monocytic marker CD11b to be independently associated with poor outcomes and closely related with MK+ and older age at diagnosis(28). Analysis of multidrug resistant (MDR) functional activity among 23 patients with MK+AML demonstrated a high frequency of MDR compared to other AML subgroups and helps explain the aggressive behavior (29). Another association of MK+AML is mutations in the tumor-suppressor gene neurofibromatosis-1 (NF-1) manifested through somatic deletions of 17q11 (30). NF-1 mutations present in AML are also associated with poor outcomes. MK+ appears to be a surrogate marker for genomic instability in AML subclones where the absence of important tumor suppressor and cell cycle checkpoint genes helps confer a survival and proliferative advantage over other subclones.

MK+ AML yields low rates (only 20 to 30%) of CR and short remission duration yielding reported median survival of 8 to 10 months with 2 year survival less than 10% (3, 13, 20, 31, 32). The current HCT study includes only those achieving CR after induction therapy. Despite worse outcomes compared to other cytogenetic groups, the overall survival for MK +AML is 29% at 3 years, substantially better than reported without transplant. In fact, Cornelissen et al compared post remission therapies among 107 patients with MK+AML who received either an allogeneic HCT (N=45), autologous HCT or chemotherapy consolidation(33). Five-year overall survival after an allogeneic HCT was 19% versus only 8% with other therapy. Multivariate analysis demonstrated a 70% reduction of relapse with an allogeneic transplant.

Following HCT, Armand et al analyzed a large cohort from the CIBMTR to determine cytogenetic groups that would influence outcomes after HCT(34). This analysis separates patients in three groups identifying inv(16) and complex cytogenetics with >4 abnormalities as the extremes of favorable and unfavorable prognosis, respectively. MK+ AML has been consistently associated with high disease relapse and poor survival after an allogeneic HCT (14, 17, 20, 31, 33, 35–37). However many of MK+ patients are not eligible for MA regimens due to their age. RIC/NMA regimens is associated with higher rates of relapse, especially in patients with poor risk cytogenetics (10, 11). In the current analysis, for MK+ disease, even with MA regimens the outcomes were worse when compared to other cytogenetic groups.

Abnormalities with chromosome 7 were the most frequently observed and we observed that MK+ was prognostically worse than chromosome 7 abnormalities without MK+ (12, 37). The use of growth factors post transplant was tested in the current study because of reports that granulocyte colony-stimulating factor preferentially induces proliferation of cells with monosomy 7 (38). The early use of growth factor (planned to be given in the first 12 days of transplant) in AML was associated with higher TRM (RR 1.32, p<001) while in MDS it was associated with lower incidence of disease relapse (RR 0.79, p=0.01). The subset analyses focused on chromosome 7 abnormalities showed no further associations with growth factor use. G-CSF expression is increased in CD34+ cells with monosomy 7(38), which could theoretically may increase the risk of disease relapse. The relationship of growth factor used early in transplantation needs to be further evaluated related to timing and type of disease being treated.

MK+ MDS as a high risk subgroup is less well established, though MK+ and chromosome 7 abnormalities (20, 37) can also influence MDS outcomes. Cytogenetics is an integral component of the IPSS (4) and the new revised IPSS (5). The revised IPSS cytogenetics include very poor cytogenetics as complex (>3) cytogenetic abnormalities which are associated with MK+. Xing et al analyzed outcomes of MDS patients showing complex karyotype and MK+ yielding similar poor outcomes(39). The revised IPSS confirmed poor prognosis for the very poor cytogenetics category (40). MK+MDS after allogeneic HCT has been described with similar poor outcomes (41–44). The current analysis also demonstrated that MK+MDS were associated with higher TRM, in contrast to the models in AML in which the cytogenetic group had no impact on TRM. These results could possibly be explained by the fact that a larger proportion of patients with MK+MDS had intermediate-II or high IPSS compared to other groups, which would require more treatment prior to transplant than other MDS groups, although this is speculative. MK+ AML and MDS are high risk groups with disappointing survival, even after allogeneic transplant. Implementing interventions after transplant to further reduce disease relapse through additional targeted therapy (45) or by optimizing graft-versus leukemia are needed to improve outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix Tables

Table A

Multivariate analysis of **relapse** for **AML, by monosomal karyotype**

		Relative Risk	P-value
Main effect			
Normal	641	1.00[a]	$P_{overall} < 0.001$
MK positive	238	1.98 (1.58–2.49)	< 0.001
Other unfavorable	1133	1.36 (1.14–1.63)	< 0.001
Intermediate	1568	0.90 (0.75–1.08)	0.27
Other significant covariates:			
Age at transplant by conditioning intensity, years			
0–20 MA	470	1.00[a]	$P_{overall} < 0.001$
21–40 MA	810	0.84 (0.68–1.04)	0.11
41–60 MA	1221	0.96 (0.78–1.19)	0.73
41–60 RIC/NMA	457	1.66 (1.31–2.10)	< 0.001
61–64 RIC/NMA	241	1.65 (1.25–2.16)	< 0.001
> 64 RIC/NMA	187	1.82 (1.37–2.44)	< 0.001
Others	194	1.01 (0.73–1.38)	0.97
Karnofsky score			
90–100%	2550	1.00[a]	$P_{overall} = 0.006$
< 90%	898	1.24 (1.09–1.42)	0.001
Missing	132	1.10 (0.82–1.48)	0.53
Graft type			
Bone marrow	1046	1.00[a]	
Peripheral blood	2534	0.84 (0.73–0.98)	0.02
Year of transplant			
Continuous	3580	1.04 (1.00–1.08)	0.07
Contrast			
Main effect MK positive vs. other unfavorable		1.46 (1.19–1.79)	< 0.001
Main effect MK positive vs. intermediate		2.20 (1.78–2.72)	< 0.001
Main effect other unfavorable vs. intermediate		1.51 (1.32–1.74)	< 0.001
Age 21–40 MA vs. 41–60 MA		0.87 (0.73–1.03)	0.11
Age 21–40 MA vs. 41–60 RIC/NMA		0.50 (0.41–0.62)	< 0.001
Age 21–40 MA vs. 61–64 RIC/NMA		0.51 (0.40–0.65)	< 0.001
Age 21–40 MA vs. > 64 RIC/NMA		0.46 (0.35–0.60)	< 0.001
Age 21–40 MA vs. others		0.83 (0.62–1.12)	0.23
Age 41–60 MA vs. 41–60 RIC/NMA		0.58 (0.49–0.69)	< 0.001
Age 41–60 MA vs. 61–64 RIC/NMA		0.59 (0.47–0.73)	< 0.001
Age 41–60 MA vs. > 64 RIC/NMA		0.53 (0.42–0.67)	< 0.001
Age 41–60 MA vs. others		0.96 (0.72–1.27)	0.77
Age 41–60 RIC/NMA vs. 61–64 RIC/NMA		1.01 (0.79–1.29)	0.94
Age 41–60 RIC/NMA vs. > 64 RIC/NMA		0.91 (0.70–1.18)	0.48

	Relative Risk	P-value
Age 41–60 RIC/NMA vs. others	1.65 (1.22–2.23)	0.001
Age 61–64 RIC/NMA vs. > 64 RIC/NMA	0.90 (0.68–1.20)	0.48
Age 61–64 RIC/NMA vs. others	1.64 (1.17–2.28)	0.004
Age > 64 RIC/NMA vs. others	1.81 (1.29–2.55)	< 0.001
Karnofsky score < 90% vs. missing	1.13 (0.83–1.54)	0.43

[a] Reference group

Table B

Multivariate analysis of **relapse** for **MDS, by monosomal karyotype**

		Relative Risk	P-value
Main effect:			
Normal	237	1.00[a]	$P_{overall}$ < 0.001
MK positive	219	2.39 (1.74–3.29)	< 0.001
Other unfavorable	416	1.50 (1.11–2.04)	0.009
Intermediate	606	1.12 (0.84–1.51)	0.44
Favorable	97	1.19 (0.76–1.86)	0.44
Other significant covariates:			
Age at transplant by conditioning intensity, years			
0–20 MA	132	1.00[a]	$P_{overall}$ < 0.001
21–40 MA	210	1.04 (0.66–1.63)	0.88
41–60 MA	512	1.79 (1.20–2.67)	0.004
41–60 RIC/NMA	277	2.66 (1.69–4.18)	< 0.001
61–64 RIC/NMA	158	2.29 (1.40–3.75)	0.001
> 64 RIC/NMA	113	3.21 (1.89–5.43)	< 0.001
Others	173	1.88 (1.17–3.01)	0.008
Karnofsky score			
90–100%	1032	1.00[a]	$P_{overall}$ = 0.04
< 90%	476	1.27 (1.04–1.54)	0.02
Missing	67	1.28 (0.85–1.92)	0.24
Conditioning regimen classification			
TBI + Cy +- others	233	1.00[a]	$P_{overall}$ < 0.001
TBI +- others	150	0.84 (0.56–1.27)	0.41
Bu + Cy +- others	506	0.86 (0.64–1.15)	0.30
Bu + Flud +- others	446	1.02 (0.74–1.40)	0.90
Flud + Mel +- others	153	0.37 (0.23–0.59)	< 0.001
Other conditioning regimen	87	1.29 (0.83–2.00)	0.27
Graft type			
Bone marrow	439	1.00[a]	
Peripheral blood	1136	0.70 (0.56–0.87)	0.002
ATG/Alemtuzumab for conditioning or GVHD prophylaxis			
ATG alone	447	1.00[a]	$P_{overall}$ = 0.005
Alemtuzumab alone	54	1.76 (1.15–2.69)	0.009

		Relative Risk	P-value
No ATG or Alemtuzumab	1074	0.89 (0.72–1.09)	0.25
Planned GM or GCSF (12 days)[b]			
No	876	1.00[a]	
Yes	699	0.79 (0.66–0.95)	0.01
Disease status at transplant			
Early	642	1.00[a]	
Advanced	933	1.75 (1.44–2.12)	< 0.001
Contrast			
Main effect MK positive vs. other unfavorable		1.59 (1.21–2.09)	< 0.001
Main effect MK positive vs. intermediate		2.13 (1.64–2.76)	< 0.001
Main effect MK positive vs. favorable		2.01 (1.32–3.06)	0.001
Main effect other unfavorable vs. intermediate		1.34 (1.06–1.69)	0.01
Main effect other unfavorable vs. favorable		1.26 (0.84–1.90)	0.27
Main effect intermediate vs. favorable		0.94 (0.63–1.41)	0.78
Age 21–40 MA vs. 41–60 MA		0.58 (0.41–0.81)	0.001
Age 21–40 MA vs. 41–60 RIC/NMA		0.39 (0.26–0.58)	< 0.001
Age 21–40 MA vs. 61–64 RIC/NMA		0.45 (0.29–0.70)	< 0.001
Age 21–40 MA vs. > 64 RIC/NMA		0.32 (0.20–0.52)	< 0.001
Age 21–40 MA vs. others		0.55 (0.36–0.84)	0.005
Age 41–60 MA vs. 41–60 RIC/NMA		0.67 (0.51–0.90)	0.007
Age 41–60 MA vs. 61–64 RIC/NMA		0.78 (0.56–1.10)	0.16
Age 41–60 MA vs. > 64 RIC/NMA		0.56 (0.38–0.82)	0.003
Age 41–60 MA vs. others		0.95 (0.69–1.32)	0.77
Age 41–60 RIC/NMA vs. 61–64 RIC/NMA		1.16 (0.83–1.62)	0.37
Age 41–60 RIC/NMA vs. > 64 RIC/NMA		0.83 (0.57–1.20)	0.32
Age 41–60 RIC/NMA vs. others		1.42 (1.00–2.00)	0.05
Age 61–64 RIC/NMA vs. > 64 RIC/NMA		0.71 (0.47–1.08)	0.11
Age 61–64 RIC/NMA vs. others		1.22 (0.82–1.81)	0.33
Age > 64 RIC/NMA vs. others		1.71 (1.12–2.61)	0.01
Karnofsky score < 90% vs. missing		0.99 (0.65–1.51)	0.97
Conditioning TBI +- others vs. Bu + Cy +- others		0.98 (0.67–1.42)	0.91
Conditioning TBI +- others vs. Bu + Flud +- others		0.82 (0.58–1.16)	0.26
Conditioning TBI +- others vs. Flud + Mel +- others		2.28 (1.43–3.63)	< 0.001
Conditioning TBI +- others vs. other		0.65 (0.42–1.01)	0.06
Conditioning Bu + Cy +- others vs. Bu + Flud +- others		0.84 (0.65–1.09)	0.19
Conditioning Bu + Cy +- others vs. Flud + Mel +- others		2.33 (1.49–3.63)	< 0.001
Conditioning Bu + Cy +- others vs. other		0.67 (0.44–1.00)	0.05
Conditioning Bu + Flud +- others vs. Flud+Mel+- others		2.77 (1.85–4.16)	< 0.001
Conditioning Bu + Flud +- others vs. other		0.79 (0.55–1.15)	0.22
Conditioning Flud + Mel +- others vs. other		0.29 (0.17–0.47)	< 0.001
Alemtuzumab alone vs. No ATG or Alemtuzumab		1.98 (1.31–3.01)	0.001

[a] Reference group

[b] GF within 7d: RR=0.82, p<0.001

Table C

Multivariate analysis of **treatment-related mortality** for **AML, by monosomal karyotype**

	N	Relative Risk	P-value
Main effect:			
Normal	641	1.00[a]	$P_{overall}$ = 0.41
MK positive	238	1.01 (0.74–1.39)	0.94
Other unfavorable	1133	0.95 (0.77–1.18)	0.66
Intermediate	1568	0.86 (0.70–1.06)	0.16
Other significant covariates:			
Age at transplant by conditioning intensity, years			
0–20 MA	470	1.00[a]	$P_{overall}$ < 0.001
21–40 MA	810	1.46 (1.06–2.02)	0.02
41–60 MA	1221	2.09 (1.53–2.83)	< 0.001
41–60 RIC/NMA	457	2.03 (1.39–2.96)	< 0.001
61–64 RIC/NMA	241	2.61 (1.72–3.94)	< 0.001
> 64 RIC/NMA	187	2.61 (1.69–4.03)	< 0.001
Others	194	1.88 (1.24–2.86)	0.003
Karnofsky score			0.001
90–100%	2550	1.00[a]	
< 90%	898	1.32 (1.13–1.54)	$P_{overall}$ < 0.001
Missing	132	1.31 (0.94–1.82)	0.11
Conditioning regimen classification			0.04
TBI + Cy +- others	911	1.00[a]	
TBI +- others	315	0.85 (0.63–1.16)	0.31
Bu + Cy +- others	1198	0.83 (0.69–1.01)	0.06
Bu + Flud +- others	802	0.72 (0.57–0.90)	0.004
Flud + Mel +- others	203	0.95 (0.68–1.32)	0.77
Other conditioning regimen	151	0.68 (0.45–1.02)	0.06
HLA matching			
HLA-identical sibling	1864	1.00[a]	$P_{overall}$ < 0.001
Unrelated 8/8	1269	1.45 (1.23–1.71)	< 0.001
Unrelated 7/8	447	2.13 (1.75–2.60)	< 0.001
Graft type			
Bone marrow	1046	1.00[a]	$P_{overall}$ = 0.002
Peripheral blood	2534	1.33 (1.11–1.61)	0.002
GVHD prophylaxis			
CNI based with Methotrexate	2545	1.00[a]	$P_{overall}$ = 0.03
CNI based with MMF	586	1.34 (1.10–1.64)	0.004
CNI +- others	371	1.20 (0.95–1.51)	0.12
Other GVHD prophylaxis	78	1.13 (0.68–1.87)	0.63
Planned GM or GCSF (within 12 days from transplant)[b]			
No	2088	1.00[a]	$P_{overall}$ < 0.001
Yes	1492	1.32 (1.15–1.52)	< 0.001

	N	Relative Risk	P-value
Year of transplant			< 0.001
Continuous	3580	0.88 (0.84–0.92)	< 0.001
Contrast			
Main effect MK positive vs. other unfavorable		1.06 (0.79–1.43)	0.69
Main effect MK positive vs. intermediate		1.18 (0.88–1.59)	0.28
Main effect other unfavorable vs. intermediate		1.11 (0.94–1.31)	0.22
Age 21–40 MA vs. 41–60 MA		0.70 (0.58–0.85)	< 0.001
Age 21–40 MA vs. 41–60 RIC/NMA		0.72 (0.54–0.96)	0.03
Age 21–40 MA vs. 61–64 RIC/NMA		0.56 (0.40–0.79)	< 0.001
Age 21–40 MA vs. > 64 RIC/NMA		0.56 (0.39–0.80)	0.002
Age 21–40 MA vs. others		0.78 (0.55–1.10)	0.15
Age 41–60 MA vs. 41–60 RIC/NMA		1.03 (0.79–1.34)	0.83
Age 41–60 MA vs. 61–64 RIC/NMA		0.80 (0.59–1.09)	0.16
Age 41–60 MA vs. > 64 RIC/NMA		0.80 (0.57–1.11)	0.19
Age 41–60 MA vs. others		1.11 (0.80–1.53)	0.54
Age 41–60 RIC/NMA vs. 61–64 RIC/NMA		0.78 (0.57–1.06)	0.11
Age 41–60 RIC/NMA vs. > 64 RIC/NMA		0.78 (0.56–1.08)	0.13
Age 41–60 RIC/NMA vs. others		1.08 (0.76–1.52)	0.68
Age 61–64 RIC/NMA vs. > 64 RIC/NMA		1.00 (0.70–1.43)	0.99
Age 61–64 RIC/NMA vs. others		1.38 (0.94–2.03)	0.10
Age > 64 RIC/NMA vs. others		1.38 (0.93–2.07)	0.11
Karnofsky score < 90% vs. missing		1.01 (0.71–1.42)	0.97
Conditioning TBI +- others vs. Bu + Cy +- others		1.02 (0.75–1.39)	0.89
Conditioning TBI +- others vs. Bu + Flud +- others		1.19 (0.89–1.59)	0.23
Conditioning TBI +- others vs. Flud + Mel +- others		0.90 (0.65–1.24)	0.51
Conditioning TBI +- others vs. other conditioning		1.26 (0.84–1.88)	0.27
Conditioning Bu + Cy +- others vs. Bu + Flud +- others		1.17 (0.93–1.47)	0.19
Conditioning Bu + Cy +- others vs. Flud + Mel +- others		0.88 (0.63–1.22)	0.43
Conditioning Bu + Cy +- others vs. other conditioning		1.23 (0.82–1.84)	0.32
Conditioning Bu + Flud +- others vs. Flud/Mel +- others		0.75 (0.56–1.01)	0.06
Conditioning Bu + Flud +- others vs. other conditioning		1.05 (0.72–1.55)	0.79
Conditioning Flud + Mel +- others vs. other conditioning		1.40 (0.93–2.12)	0.11
HLA matching 8/8 vs. 7/8		0.68 (0.56–0.82)	< 0.001
GVHD prophylaxis CNI based+MMF vs. CNI +- others		1.12 (0.86–1.46)	0.41
GVHD prophylaxis CNI based with MMF vs. other		1.19 (0.70–2.01)	0.53
GVHD prophylaxis CNI +- others vs. other		1.06 (0.62–1.82)	0.83

[a] Reference group

[b] GF within 7d: RR=1.39, p<0.001

Table D

Multivariate analysis of **treatment-related mortality** for **MDS, by monosomal karyotype**

		Relative Risk	P-value
Main effect:			
Normal	237	1.00[a]	$P_{overall} < 0.001$
MK positive	219	1.80 (1.27–2.54)	< 0.001
Other unfavorable	416	1.37 (0.99–1.90)	0.06
Intermediate	606	1.01 (0.73–1.39)	0.97
Favorable	97	0.95 (0.59–1.52)	0.83
Other significant covariates:			
Age at transplant by conditioning intensity, years			
0–20 MA	132	1.00[a]	$P_{overall} < 0.001$
21–40 MA	210	1.62 (1.01–2.58)	0.04
41–60 MA	512	2.30 (1.50–3.54)	< 0.001
41–60 RIC/NMA	277	2.41 (1.53–3.79)	< 0.001
61–64 RIC/NMA	158	2.18 (1.33–3.57)	0.002
> 64 RIC/NMA	113	2.69 (1.56–4.66)	< 0.001
Others	173	2.67 (1.65–4.34)	< 0.001
Karnofsky score			
90–100%	1032	1.00[a]	$P_{overall} = 0.003$
< 90%	476	1.40 (1.16–1.70)	< 0.001
Missing	67	1.20 (0.78–1.87)	0.41
HLA matching			
HLA-identical sibling	662	1.00[a]	$P_{overall} < 0.001$
Unrelated 8/8	704	1.11 (0.90–1.36)	0.32
Unrelated 7/8	209	1.74 (1.34–2.26)	< 0.001
Disease status at transplant			
Early	642	1.00[a]	
Advanced	933	1.30 (1.08–1.58)	0.006
Year of transplant			
Continuous	1575	0.91 (0.86–0.96)	< 0.001
Contrast			
Main effect MK positive vs. other unfavorable		1.31 (0.98–1.76)	0.07
Main effect MK positive vs. intermediate		1.79 (1.34–2.38)	< 0.001
Main effect MK positive vs. favorable		1.89 (1.22–2.94)	0.005
Main effect other unfavorable vs. intermediate		1.36 (1.08–1.71)	0.009
Main effect other unfavorable vs. favorable		1.44 (0.96–2.17)	0.08
Main effect intermediate vs. favorable		1.06 (0.71–1.58)	0.78
Age 21–40 MA vs. 41–60 MA		0.70 (0.52–0.95)	0.02
Age 21–40 MA vs. 41–60 RIC/NMA		0.67 (0.48–0.94)	0.02
Age 21–40 MA vs. 61–64 RIC/NMA		0.74 (0.50–1.09)	0.13
Age 21–40 MA vs. > 64 RIC/NMA		0.60 (0.38–0.95)	0.03

	Relative Risk	P-value
Age 21–40 MA vs. others	0.61 (0.42–0.88)	0.009
Age 41–60 MA vs. 41–60 RIC/NMA	0.96 (0.73–1.25)	0.74
Age 41–60 MA vs. 61–64 RIC/NMA	1.06 (0.77–1.46)	0.74
Age 41–60 MA vs. > 64 RIC/NMA	0.85 (0.58–1.27)	0.43
Age 41–60 MA vs. others	0.86 (0.63–1.17)	0.34
Age 41–60 RIC/NMA vs. 61–64 RIC/NMA	1.10 (0.77–1.57)	0.58
Age 41–60 RIC/NMA vs. > 64 RIC/NMA	0.89 (0.59–1.36)	0.60
Age 41–60 RIC/NMA vs. others	0.90 (0.64–1.27)	0.55
Age 61–64 RIC/NMA vs. > 64 RIC/NMA	0.81 (0.51–1.28)	0.36
Age 61–64 RIC/NMA vs. others	0.82 (0.56–1.20)	0.30
Age > 64 RIC/NMA vs. others	1.01 (0.65–1.57)	0.97
Karnofsky score < 90% vs. missing	1.17 (0.74–1.83)	0.50
HLA matching 8/8 vs. 7/8	0.64 (0.49–0.83)	< 0.001

[a] Reference group

Table E

Multivariate analysis of **overall survival** for **AML, by monosomal karyotype**

		Relative Risk of Death	P-value
Main effect:			
Normal	643	1.00[a]	$P_{overall}$ < 0.001
MK positive	240	1.67 (1.38–2.01)	< 0.001
Other unfavorable	1138	1.22 (1.06–1.40)	0.006
Intermediate	1579	0.90 (0.78–1.05)	0.17
Other significant covariates:			
Age at transplant by conditioning intensity, years			
0–20 MA	474	1.00[a]	$P_{overall}$ < 0.001
21–40 MA	811	1.06 (0.89–1.27)	0.50
41–60 MA	1228	1.43 (1.21–1.69)	< 0.001
41–60 RIC/NMA	461	1.85 (1.53–2.23)	< 0.001
61–64 RIC/NMA	241	2.10 (1.69–2.61)	< 0.001
> 64 RIC/NMA	189	2.16 (1.72–2.72)	< 0.001
Others	196	1.29 (1.01–1.66)	0.04
Karnofsky score			
90–100%	2562	1.00[a]	$P_{overall}$ < 0.001
< 90%	906	1.30 (1.17–1.44)	< 0.001
Missing	132	1.22 (0.98–1.53)	0.07
HLA matching			
HLA-identical sibling	1873	1.00[a]	$P_{overall}$ < 0.001
Unrelated 8/8	1276	1.18 (1.06–1.31)	0.002
Unrelated 7/8	451	1.48 (1.29–1.70)	< 0.001
Year of transplant			
Continuous	3600	0.95 (0.93–0.98)	0.002

	Relative Risk of Death	P-value
Contrast		
Main effect MK positive vs. other unfavorable	1.37 (1.15–1.62)	< 0.001
Main effect MK positive vs. intermediate	1.84 (1.55–2.19)	< 0.001
Main effect other unfavorable vs. intermediate	1.35 (1.20–1.50)	< 0.001
Age 21–40 MA vs. 41–60 MA	0.74 (0.65–0.85)	< 0.001
Age 21–40 MA vs. 41–60 RIC/NMA	0.58 (0.49–0.68)	< 0.001
Age 21–40 MA vs. 61–64 RIC/NMA	0.51 (0.42–0.61)	< 0.001
Age 21–40 MA vs. > 64 RIC/NMA	0.49 (0.40–0.60)	< 0.001
Age 21–40 MA vs. others	0.82 (0.65–1.04)	0.10
Age 41–60 MA vs. 41–60 RIC/NMA	0.77 (0.67–0.89)	< 0.001
Age 41–60 MA vs. 61–64 RIC/NMA	0.68 (0.57–0.81)	< 0.001
Age 41–60 MA vs. > 64 RIC/NMA	0.66 (0.55–0.80)	< 0.001
Age 41–60 MA vs. others	1.11 (0.89–1.38)	0.36
Age 41–60 RIC/NMA vs. 61–64 RIC/NMA	0.88 (0.72–1.07)	0.19
Age 41–60 RIC/NMA vs. > 64 RIC/NMA	0.85 (0.69–1.05)	0.13
Age 41–60 RIC/NMA vs. others	1.43 (1.13–1.81)	0.003
Age 61–64 RIC/NMA vs. > 64 RIC/NMA	0.97 (0.77–1.22)	0.80
Age 61–64 RIC/NMA vs. others	1.63 (1.26–2.10)	< 0.001
Age > 64 RIC/NMA vs. others	1.67 (1.28–2.19)	< 0.001
Karnofsky score < 90% vs. missing	1.06 (0.84–1.34)	0.62
HLA matching 8/8 vs. 7/8	0.80 (0.69–0.91)	0.001

[a] Reference group

Table F

Multivariate analysis of **overall survival** for **MDS, by monosomal karyotype**

		Relative Risk of death	P-value
Main effect:			
Normal	241	1.00[a]	$P_{overall}$ < 0.001
MK positive	221	2.02 (1.59–2.59)	< 0.001
Other unfavorable	423	1.39 (1.10–1.77)	0.006
Intermediate	611	0.96 (0.76–1.22)	0.73
Favorable	98	1.00 (0.71–1.41)	1.00
Other significant covariates:			
Age at transplant by conditioning intensity, years			
0–20 MA	132	1.00[a]	$P_{overall}$ < 0.001
21–40 MA	212	1.32 (0.93–1.86)	0.12
41–60 MA	519	2.08 (1.52–2.83)	< 0.001
41–60 RIC/NMA	281	2.18 (1.57–3.02)	< 0.001
61–64 RIC/NMA	160	2.05 (1.44–2.91)	< 0.001
> 64 RIC/NMA	116	2.70 (1.83–3.97)	< 0.001
Others	174	2.13 (1.50–3.04)	< 0.001

		Relative Risk of death	P-value
Karnofsky score			
90–100%	1041	1.00[a]	$P_{overall}$ < 0.001
< 90%	484	1.40 (1.22–1.62)	< 0.001
Missing	69	1.34 (0.99–1.82)	0.06
HLA matching			
HLA-identical sibling	668	1.00[a]	$P_{overall}$ < 0.001
Unrelated 8/8	712	1.09 (0.94–1.27)	0.26
Unrelated 7/8	214	1.62 (1.34–1.97)	< 0.001
Disease status at transplant			
Early	652	1.00[a]	
Advanced	942	1.45 (1.26–1.67)	< 0.001
Year of transplant			
Continuous	1594	0.94 (0.90–0.98)	0.004
Contrast			
Main effect MK positive vs. other unfavorable		1.45 (1.19–1.78)	< 0.001
Main effect MK positive vs. intermediate		2.11 (1.73–2.58)	< 0.001
Main effect MK positive vs. favorable		2.02 (1.48–2.78)	< 0.001
Main effect other unfavorable vs. intermediate		1.45 (1.22–1.72)	< 0.001
Main effect other unfavorable vs. favorable		1.39 (1.03–1.88)	0.03
Main effect intermediate vs. favorable		0.96 (0.71–1.29)	0.78
Age 21–40 MA vs. 41–60 MA		0.63 (0.50–0.80)	< 0.001
Age 21–40 MA vs. 41–60 RIC/NMA		0.60 (0.47–0.78)	< 0.001
Age 21–40 MA vs. 61–64 RIC/NMA		0.64 (0.48–0.86)	0.003
Age 21–40 MA vs. > 64 RIC/NMA		0.49 (0.35–0.68)	< 0.001
Age 21–40 MA vs. others		0.62 (0.46–0.82)	0.001
Age 41–60 MA vs. 41–60 RIC/NMA		0.95 (0.79–1.15)	0.62
Age 41–60 MA vs. 61–64 RIC/NMA		1.01 (0.81–1.28)	0.90
Age 41–60 MA vs. > 64 RIC/NMA		0.77 (0.59–1.01)	0.06
Age 41–60 MA vs. others		0.97 (0.77–1.23)	0.82
Age 41–60 RIC/NMA vs. 61–64 RIC/NMA		1.06 (0.83–1.37)	0.63
Age 41–60 RIC/NMA vs. > 64 RIC/NMA		0.81 (0.60–1.08)	0.15
Age 41–60 RIC/NMA vs. others		1.02 (0.79–1.32)	0.86
Age 61–64 RIC/NMA vs. > 64 RIC/NMA		0.76 (0.55–1.04)	0.09
Age 61–64 RIC/NMA vs. others		0.96 (0.72–1.27)	0.78
Age > 64 RIC/NMA vs. others		1.27 (0.92–1.74)	0.14
Karnofsky score < 90% vs. missing		1.05 (0.77–1.43)	0.77
HLA matching 8/8 vs. 7/8		0.67 (0.55–0.81)	< 0.001

[a]Reference group

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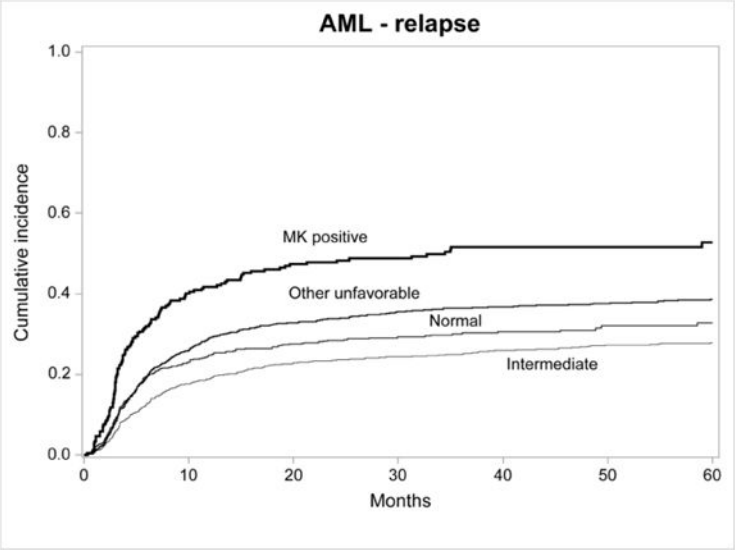
The Highlights for this study include

1. Patients with MK+ AML have worse survival after transplant compared to other AML in CR1.
2. MK+ in patients with MDS has a negative prognostic impact after allogeneic transplant.
3. The negative impact of MK+ is observed after myeloablative and reduced intensity conditioning

A



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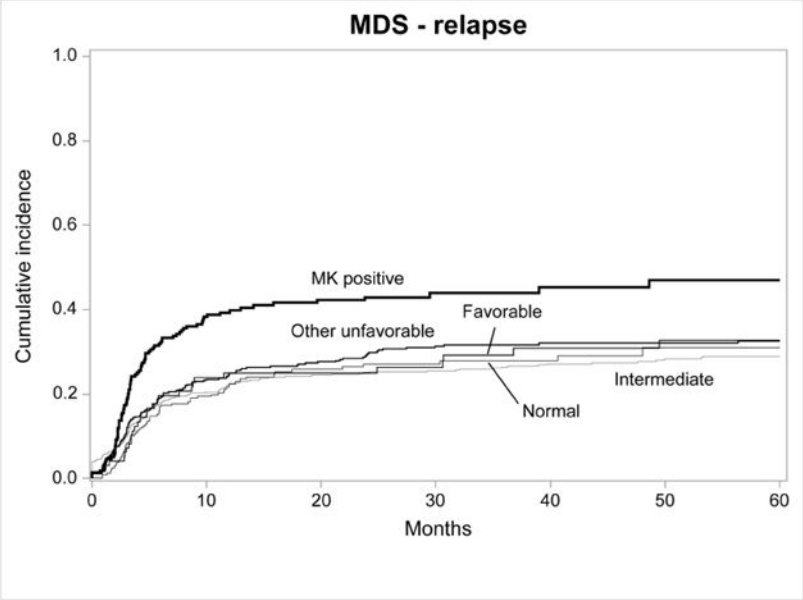

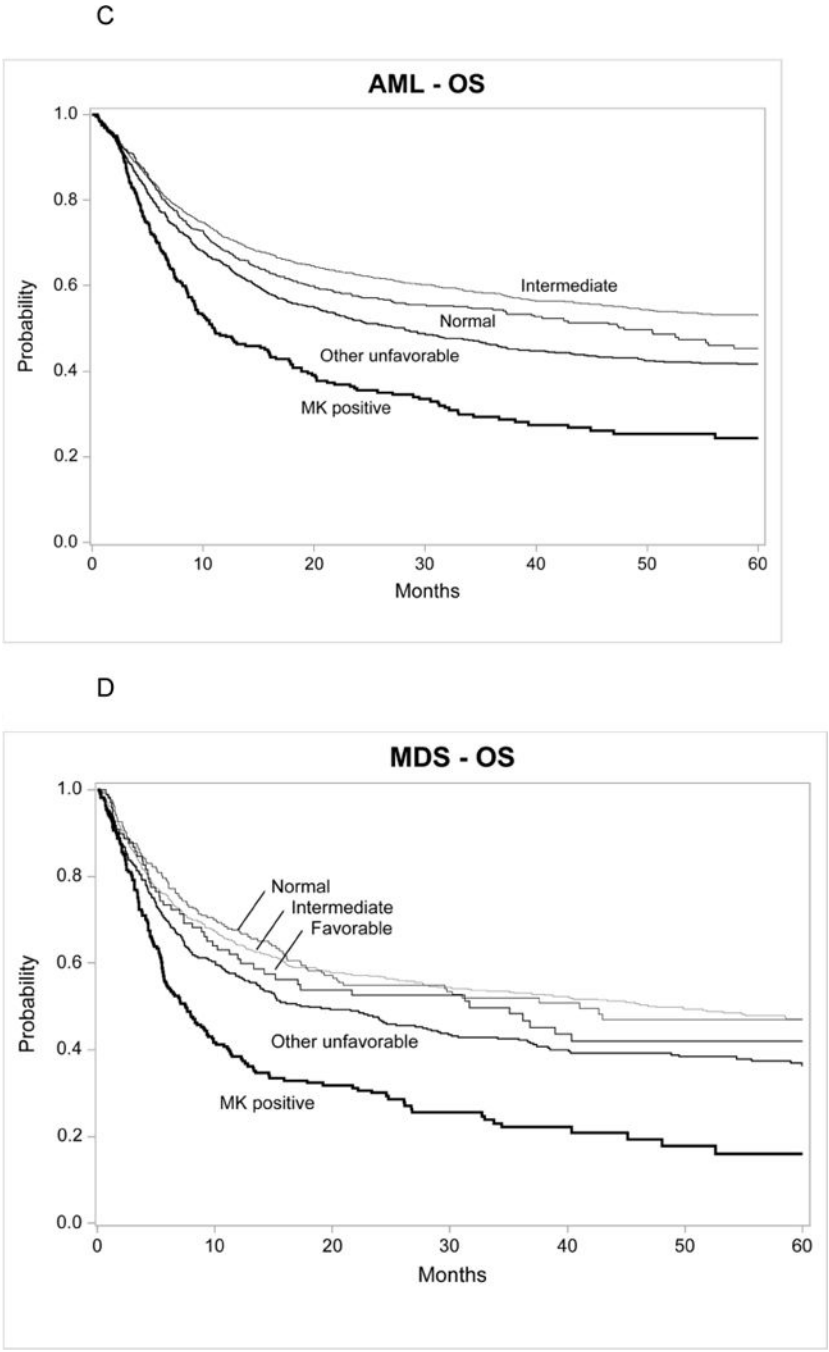

Figure 1.

Cumulative incidence of disease relapse for AML in first complete remission(1A) and MDS (1B) and overall survival for AML in first complete remission (1C) and MDS (1D) after HCT,

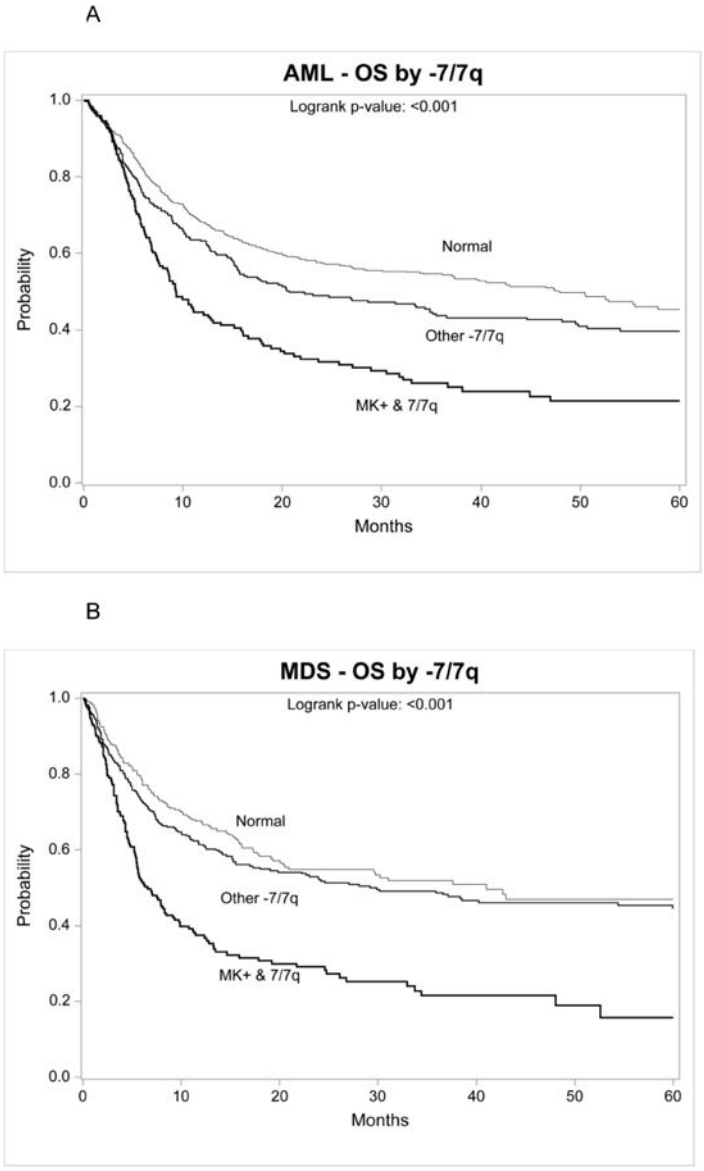

Figure 2.

Overall survival for AML in first complete remission (2A) and MDS (2B) after HCT defined as chromosome 7 abnormalities with or without monosomal karyotype (MK+) and normal karyotype

Table 1a

Demographic data on hematopoietic cell transplant recipients with AML from 1998–2011 according to cytogenetic groups.

Variable	MK positive	Other unfavorable	Intermediate	Normal
Number of patients	240	1138	1579	643
Number of centers	80	192	224	138
Age at transplant, median (years)	53 (1–75)	43 (1–76)	43 (<1–74)	52 (2–74)
Age at transplant, years				
0–20	13 (5)	192 (17)	255 (16)	49 (8)
21–40	45 (19)	302 (27)	432 (27)	107 (17)
41–60	123 (51)	496 (44)	738 (47)	332 (52)
61–64	30 (13)	94 (8)	97 (6)	87 (14)
>= 65	29 (12)	54 (5)	57 (4)	68 (11)
Gender				
Male	146 (61)	572 (50)	816 (52)	324 (50)
Female	94 (39)	566 (50)	763 (48)	319 (50)
Performance Score				
90–100%	134 (56)	798 (70)	1186 (75)	444 (69)
< 90%	90 (38)	293 (26)	338 (21)	185 (29)
Missing	16 (7)	47 (4)	55 (3)	14 (2)
Type of AML				
De novo	168 (70)	848 (75)	1256 (80)	454 (71)
Secondary	71 (30)	288 (25)	316 (20)	188 (29)
Unknown	1 (<1)	2 (<1)	7 (<1)	1 (<1)
Number of cycles to achieve CR				
1	67 (28)	385 (34)	785 (50)	240 (37)
> 1	65 (27)	260 (23)	386 (24)	176 (27)
Unknown	108 (45)	493 (43)	408 (26)	227 (35)
Extra medullary disease				
No	227 (95)	1058 (93)	1446 (92)	584 (91)
Yes	13 (5)	80 (7)	133 (8)	59 (9)
White blood cell at diagnosis (median, ×10^9/L)	3 (<1–53)	6 (<1–224)	9 (<1–118)	10 (<1–260)
Cytogenetic score				
Normal	0	0	0	643
Intermediate	0	0	1579	0
Poor	240	1138	0	0
MK status				
MK+: more than 1 monosomy	136 (57)	0	0	0
MK+: 1 monosomy + other	104 (43)	0	0	0
Other	0	1138	1578	643
Abnormality −7/7q				
No	92 (38)	863 (76)	1579	643

Variable	MK positive	Other unfavorable	Intermediate	Normal
Yes	148 (62)	275 (24)	0	0
Conditioning regimen				
TBI + Cy +- others	48 (20)	320 (28)	392 (25)	156 (24)
TBI +- others	28 (12)	72 (6)	156 (10)	62 (10)
Bu + Cy +- others	57 (24)	389 (34)	611 (39)	147 (23)
Bu + Flud +- others	73 (30)	236 (21)	278 (18)	217 (34)
Flud + Mel +- others	21 (9)	77 (7)	74 (5)	34 (5)
Other conditioning regimen	13 (5)	44 (4)	68 (4)	27 (4)
Conditioning regimen intensity				
Myeloablative	139 (58)	857 (75)	1163 (74)	440 (68)
RIC	101 (42)	281 (25)	416 (26)	203 (32)
Time from diagnosis to transplant, median (months)	5 (1–40)	5 (1–118)	5 (1–165)	5 (1–91)
Time from diagnosis to transplant				
0–3 months	17 (7)	106 (9)	188 (12)	63 (10)
3–6 months	159 (66)	723 (64)	899 (57)	385 (60)
>= 6 months	64 (27)	309 (27)	492 (31)	195 (30)
Type of donor				
HLA-identical sibling	75 (31)	481 (42)	1028 (65)	289 (45)
Unrelated 8/8	122 (51)	499 (44)	387 (25)	268 (42)
Unrelated 7/8	43 (18)	158 (14)	164 (10)	86 (13)
Missing	11 (5)	42 (4)	61 (4)	21 (3)
Graft type				
Bone marrow	46 (19)	359 (32)	523 (33)	126 (20)
Peripheral blood	194 (81)	779 (68)	1056 (67)	517 (80)
GVHD prophylaxis				
CNI plus Methotrexate	162 (68)	797 (70)	1162 (74)	439 (68)
CNI plus MMF	54 (23)	190 (17)	209 (13)	135 (21)
CNI +- others	20 (8)	125 (11)	167 (11)	60 (9)
Other	4 (2)	26 (2)	41 (3)	9 (1)
ATG/Alemtuzumab	68 (28)	308 (28)	331 (21)	178 (28)
Planned GM or GCSF (<12 days post HCT)	96 (40)	472 (41)	694 (44)	239 (37)
Median follow-up of survivors (range), months	49 (4–144)	60 (3–171)	70 (3–172)	37 (3–122)

Abbreviations: AML, acute myeloid leukemia; ATG, anti-thymocyte globulin; Bu, busulfan; CNI, calcineurin inhibitor; Cy, cyclophosphamide; Flud, fludarabine; GM/GCSF, granulocyte and macrophage or granulocyte growth factor; MK, monosomal karyotype; MMF, micophenolate mofetil; Mel; melphalan; RIC, reduced intensity conditioning; TBI, total body irradiation.

Table 1b

Demographic data on hematopoietic cell transplant recipients with MDS from 1998–2011 according to cytogenetic groups.

Variable	MK positive	Other unfavorable	Intermediate	Normal	Favorable
Number of patients	221	423	611	241	98
Number of centers	85	138	162	78	56
Age at transplant, median (years)	56 (8–74)	49 (<1–74)	50 (1–74)	57 (4–72)	54 (12–72)
Age at transplant, years					
0–20	10 (5)	67 (16)	58 (9)	8 (3)	2 (2)
21–40	26 (12)	76 (18)	122 (20)	26 (11)	10 (10)
41–60	123 (56)	189 (45)	314 (51)	117 (49)	57 (58)
61–64	33 (15)	58 (14)	80 (13)	55 (23)	15 (15)
>= 65	29 (13)	33 (8)	37 (6)	35 (15)	14 (14)
Gender					
Male	128 (58)	247 (58)	361 (59)	148 (61)	62 (63)
Female	93 (42)	176 (42)	250 (41)	93 (39)	36 (37)
Performance Score					
90–100%	120 (54)	300 (71)	405 (66)	161 (67)	55 (56)
< 90%	91 (41)	104 (25)	182 (30)	70 (29)	37 (38)
Missing	10 (5)	19 (4)	24 (4)	10 (4)	6 (6)
IPSS prior to transplant					
Low	0	0	0	101 (42)	21 (21)
Intermediate-1	63 (29)	133 (31)	400 (65)	118 (49)	61 (62)
Intermediate-2	119 (54)	202 (48)	147 (24)	7 (3)	8 (8)
High	21 (10)	29 (7)	1 (<1)	0	0
Missing	18 (8)	59 (14)	63 (10)	15 (6)	8 (8)
Bone marrow blasts prior to transplant					
< 5%	117 (53)	233 (55)	329 (54)	148 (61)	56 (57)
5–10%	59 (27)	99 (23)	155 (25)	67 (28)	26 (27)
11–20%	28 (13)	36 (9)	67 (11)	14 (6)	8 (8)
> 20%	0	6 (1)	4 (<1)	1 (<1)	1 (1)
Missing	17 (8)	49 (12)	56 (9)	11 (5)	7 (7)
Disease status at transplant					

Variable	MK positive	Other unfavorable	Intermediate	Normal	Favorable
Early	71 (32)	183 (43)	266 (44)	82 (34)	50 (51)
Advanced	150 (68)	240 (57)	345 (56)	159 (66)	48 (49)
Cytogenetic group					
Normal	0	0	0	241	0
Favorable	1 (<1)	0	0	0	98
Intermediate	6 (3)	0	611	0	0
Poor	214 (97)	423	0	0	0
Abnormality −7/7q					
No	50 (23)	119 (28)	611	241	98
Yes	171 (77)	304 (72)	0	0	0
Conditioning regimen					
TBI + Cy +- others	21 (10)	80 (19)	100 (16)	24 (10)	12 (12)
TBI +- others	22 (10)	40 (9)	61 (10)	25 (10)	4 (4)
Bu + Cy +- others	62 (28)	126 (30)	225 (37)	67 (28)	27 (28)
Bu + Flud +- others	85 (38)	110 (26)	127 (21)	92 (38)	39 (40)
Flud + Mel +- others	20 (9)	45 (11)	57 (9)	19 (8)	15 (15)
Other conditioning regimen	11 (5)	22 (5)	41 (7)	14 (6)	1 (1)
Conditioning regimen intensity					
Myeloablative	140 (63)	265 (63)	376 (62)	140 (58)	55 (56)
RIC	81 (37)	158 (37)	235 (38)	101 (42)	43 (44)
Time from diagnosis to transplant, median (months)	5 (1–187)	6 (<1–131)	8 (1–275)	9 (1–284)	12 (1–266)
Time from diagnosis to transplant					
0–3 months	22 (10)	50 (12)	59 (10)	14 (6)	5 (5)
3–6 months	104 (47)	162 (38)	161 (26)	57 (24)	19 (19)
>= 6 months	95 (43)	211 (50)	391 (64)	170 (71)	74 (76)
Type of donor					
HLA-identical sibling	69 (31)	132 (31)	331 (54)	100 (41)	36 (37)
Unrelated 8/8	122 (55)	215 (51)	204 (33)	122 (51)	49 (50)
Unrelated 7/8	30 (14)	76 (18)	76 (12)	19 (8)	13 (13)
Graft type					
Bone marrow	48 (22)	144 (34)	184 (30)	46 (19)	24 (24)

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Variable	MK positive	Other unfavorable	Intermediate	Normal	Favorable
Peripheral blood	173 (78)	279 (66)	427 (70)	195 (81)	74 (76)
GVHD prophylaxis					
CNI plus Methotrexate	138 (62)	278 (66)	396 (65)	149 (62)	66 (67)
CNI plus MMF	56 (25)	93 (22)	109 (18)	61 (25)	15 (15)
CNI +- others	18 (8)	39 (9)	95 (16)	25 (10)	17 (17)
Other	9 (4)	13 (3)	11 (2)	6 (2)	0
ATG/Campath	89 (40)	139 (33)	171 (28)	80 (33)	29 (30)
Planned GM or GCSF (<12 days post HCT)	99 (45)	185 (44)	274 (45)	104 (43)	43 (44)
Median follow-up of survivors (range), months	35 (10–96)	53 (3–171)	53 (3–174)	36 (6–72)	60 (4–167)

Abbreviations: AML, acute myeloid leukemia; ATG, anti-thymocyte globulin; Bu, busulfan; CNI, calcineurin inhibitor; Cy, cyclophosphamide; Flud, fludarabine; GM/GCSF, granulocyte and macrophage or granulocyte growth factor; MK, monosomal karyotype; MMF, micophenolate mofetil; Mel; melphalan; RIC, reduced intensity conditioning; TBI, total body irradiation.

Table 2

Multivariate analysis of treatment related mortality, relapse, treatment failure (1-LFS) and overall mortality for AML and MDS by cytogenetic groups and adjusted for significant covariates.

AML	N	Relative Risk	P-value	MDS	N	Relative Risk	P-value
TRM				TRM			
Normal	641	1.00[a]	<0.41[1]	Normal	237	1.00[a]	< 0.001[1]
MK positive	238	1.01 (0.74–1.39)	0.94	MK positive	219	1.80 (1.27–2.54)	< 0.001
Other unfavorable	1133	0.95 (0.77–1.18)	0.66	Other unfavorable	416	1.37 (0.99–1.90)	0.06
Intermediate	1568	0.86 (0.70–1.06)	0.16	Intermediate	606	1.01 (0.73–1.39)	0.97
				Favorable	97	0.95 (0.59–1.52)	0.83
Relapse				Relapse			
Normal	641	1.00[a]	< 0.001[1]	Normal	237	1.00[a]	< 0.001[1]
MK positive	238	1.98 (1.58–2.49)	< 0.001	MK positive	219	2.39 (1.74–3.29)	< 0.001
Other unfavorable	1133	1.36 (1.14–1.63)	< 0.001	Other unfavorable	416	1.50 (1.11–2.04)	0.009
Intermediate	1568	0.90 (0.75–1.08)	0.27	Intermediate	606	1.12 (0.84–1.51)	0.44
				Favorable	97	1.19 (0.76–1.86)	0.44
Treatment Failure:				Treatment Failure:			
Normal	641	1.00[a]	< 0.001[1]	Normal	237	1.00[a]	< 0.001[1]
MK positive	238	1.55 (1.29–1.86)	< 0.001	MK positive	219	2.17 (1.72–2.74)	< 0.001
Other unfavorable	1133	1.19 (1.04–1.37)	0.01	Other unfavorable	416	1.52 (1.22–1.89)	< 0.001
Intermediate	1568	0.88 (0.77–1.02)	0.09	Intermediate	606	1.13 (0.92–1.40)	0.25
				Favorable	97	1.15 (0.84–1.57)	0.40
Overall Mortality:				Overall Mortality:			
Normal	643	1.00[a]	< 0.001[1]	Normal	241	1.00[a]	< 0.001[1]
MK positive	240	1.67 (1.38–2.01)	< 0.001	MK positive	221	2.02 (1.59–2.59)	< 0.001
Other unfavorable	1138	1.22 (1.06–1.40)	0.006	Other unfavorable	423	1.39 (1.10–1.77)	0.006
Intermediate	1579	0.90 (0.78–1.05)	0.17	Intermediate	611	0.96 (0.76–1.22)	0.73
				Favorable	98	1.00 (0.71–1.41)	1.00

[1] Overall P value

[a] Reference group

Abbreviations: AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; MK, monosomal karyotype; TRM, transplant related mortality