Clinical impact of the loss of chromosome 7q on outcomes of patients with myelodysplastic syndromes treated with allogeneic hematopoietic stem cell transplantation

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Abstract

We conducted a nationwide retrospective study to evaluate the prognostic influence of +1, der(1;7)(q10;p10) [hereafter der(1;7)] and -7/del(7q) after allogeneic hematopoietic stem cell transplantation (allo-HSCT) for *de novo* myelodysplastic syndromes (MDS). In this database, 69 MDS patients with der(1;7), 75 with -7/del(7q), and 511 with normal karyotype (NK) underwent allo-HSCT at advanced disease status. The 3-year overall survival (OS) and cumulative incidence of relapse (CIR) were 50.4% and 19.4% for those with der(1;7), 36.2% and 38.4% for -7/del(7q), and 51.1% and 20.7% for NK, respectively. In the multivariate analysis, the presence of -7/del(7q) correlated with a significantly shorter OS (HR [95%CI], 1.38 [1.00-1.89]; *P*=.048) and higher CIR (HR, 2.11 [1.36-3.28]; *P*=.001) than those with NK. There were 23 patients with der(1;7), 29 with -7/del(7q), and 347 with NK who underwent allo-HSCT at early disease status. The 3-year OS and CIR were as follows: 47.3% and 9.5% for the der(1;7) group, 70.5% and 13.8% for -7/del(7q), and 70.9% and 5.6% for NK, respectively. No significant differences were observed in OS and CIR among three groups. The impact of the loss of chromosome 7q on OS and CIR may differ based on its type and disease status after allo-HSCT for MDS.

Introduction

Myelodysplastic syndromes (MDS) are clonal hematopoietic stem-cell disorders which are characterized by ineffective hematopoiesis with one or more lineages of cytopenias [1]. Acquired cytogenetic abnormalities at the time of diagnosis are one of the major and independent prognostic factors in outcome predictions for MDS. In the International Prognostic Scoring System (IPSS) [2], abnormalities on chromosome 7 have been categorized as a poor-risk karyotype, which comprises various patterns including monosomy 7, the partial deletion of 7q [del(7q)], and unbalanced translocations der(1;7)(q10;p10). In the revised IPSS [3], abnormalities on chromosome 7 have been subdivided into 3 groups (i.e. monosomy 7, del(7q), or any others), suggesting that the impact of the loss of 7q on the prognosis of MDS may differ depending on its pattern.

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is the only potentially curative therapeutic option for MDS patients, but is associated with severe toxicity [4-6]; therefore, estimations of the outcomes of patients after allo-HSCT are crucial for establishing therapeutic strategies. Among several prognostic scoring systems, cytogenetic abnormalities are the most significant indicator of post-transplant outcomes [7-10].

The International System for Human Cytogenetic Nomenclature (2005) described that

46,XY (or 46,XX), +1, der(1;7)(q10;p10) [hereafter der(1;7)] was characterized by an allelic imbalance in trisomy 1q and monosomy 7q [11]. Thus, der(1;7) is currently considered to be a "karyotypic variant" of monosomy 7 or del(7q) [hereafter -7/del(7q)]. Previous studies showed that patients with der(1;7) had different clinical and pathological features from those with -7/de(7q) [12-14]. However, due to the small number of patients who received allo-HSCT in these studies, the prognostic impact of the different types of the loss of 7q on post-transplant outcomes was not fully evaluated.

In order to more clearly estimate the post-transplant outcomes of MDS with the loss of 7q, we performed a retrospective analysis on patients with der(1;7) or -7/del(7q) who were treated with allo-HSCT using the Transplant Registry Unified Management Program (TRUMP) database.

Patients and methods

Date collection

Data on adult patients (aged 16 years or older) with *de novo* MDS who underwent their first allo-HSCT between January 1, 1999, and December 31, 2012, were collected by the Japan Society for Hematopoietic Cell Transplantation (JSHCT) and the Japanese Data Center for Hematopoietic Cell Transplantation (JDCHCT) using TRUMP [15-17]. Data

on these patients were collected and updated as of December 31, 2013. This study was approved by the TRUMP Committee (approval no. 8-7), and by the Ethics Committee of Nagasaki University Hospital (approval no. 12052896) at which this study was organized.

Patient selection

The original dataset consisted of 4,577 adults who were diagnosed with MDS according to the French–American–British (FAB) classification [18]. The patients included in the present study had a cytogenetic report at diagnosis which identified der(1;7) or -7/del(7q) as the sole clonal cytogenetic abnormality (at least two cells with an identical rearrangement). Patients with chronic myelomonocytic leukemia or secondary- and therapy-related MDS were excluded from this study. Data on 1,054 patients with MDS were collected from this dataset: 92 and 104 patients with der(1;7) and -7/del(7q) as the sole cytogenetic abnormality, respectively; 858 patients with normal karyotype, who were included in this study as a reference group.

Study end-points and definitions

The primary outcome studied was survival. Patients were considered to have an event at the time of death from any cause; survivors were censored at the last follow-up. Relapse

was defined as disease recurrence, and transplantation-related mortality (TRM) was considered to be a competing event in the present study. TRM was defined as death without evidence of disease recurrence after allo-HSCT.

The following karyotypic descriptions were regarded as der(1;7)(q10;p10), as previously reported [12]: der(1;7)(q10;p10); der(1)t(1;7)(p11;p11); +t(1;7)(p11;p11),-7; der(1;7)(p10;q10); and dic(1;7)(p11;q11).

Data collected for the analysis included clinical characteristics, such as age at allo-HSCT, gender, disease subtype according the FAB classification at diagnosis [18], IPSS at diagnosis, bone marrow blast percent at transplantation, the year of allo-HSCT, time from MDS diagnosis to transplantation, performance status (PS) according to the Eastern Cooperative Oncology Group criteria at transplantation, type of donor source, ABO matching between the recipient and donor, date alive at the last follow-up, and date and cause of death. Conditioning regimens were classified as myeloablative, reduced-intensity, and non-myeloablative conditioning according to established criteria [19, 20]. GVHD prophylaxis was a cyclosporine- or tacrolimus-based regimen. HLA-A, -B, and -DRB1 were identified by serological or molecular typing in related donors using molecular typing in unrelated bone marrow donors and serological typing in unrelated cord blood donors [21, 22]. To reflect current practices in Japan, the number of HLA

mismatches was assessed with respect to serological data in related and unrelated cord blood donors, and by allele data in unrelated bone marrow donors. Due to missing data on IPSS components at allo-HSCT in TRUMP, the disease risk was stratified according to the FAB classification as previously reported [23, 24]; early disease status contained those who had stayed refractory anemia (RA) or RA with ring sideroblasts (RARS) until allo-HSCT. Patients who were diagnosed as RA with excess blasts (RAEB) or RAEB in transformation (RAEB-t) at any time before allo-HSCT were categorized as in advanced disease status.

Statistical analysis

Continuous variables were compared using the Wilcoxon rank-sum test or Kruskal-Wallis test. Categorical variables were compared between groups using the chi-squared test. The probabilities of OS were estimated by the Kaplan-Meier method and group comparisons were performed by the log-rank test. Cumulative incidence of relapse (CIR) and TRM were estimated in a competing risk setting, and group comparisons were performed by the Gray test. Regarding relapse, death before relapse was the competing event; and for TRM, death after relapse was the competing event [25, 26]. In order to assess variables potentially affecting post-transplant outcomes, OS was evaluated using

Cox's proportional hazards regression models, whereas the probabilities of relapse and TRM were evaluated using the Fine and Gray proportional hazards model for the subdistribution of competing risks [26].

Factors associated with at least borderline significance ($P \leq .10$) in the univariate analysis and cytogenetic groups were subjected to a multivariate analysis using a backward stepwise covariate selection. Potential interactions between covariates were also examined. Effect estimates were expressed as hazard ratios (HRs) with 95% confidence intervals (CIs). All P-values were 2-tailed, and P-values $\leq .05$ were considered to be significant. All statistical analyses were performed using Stata software, version 12 (Stata, College Station, Tx, USA.), and graphical presentations were performed using EZR software, version 1.24 (Saitama Medical Center, Jichi Medical University) [27].

Results

Patient characteristics

In our entire cohort, der(1;7) group was likely to be older than -7/del(7q) and normal karyotype groups ($P<.001$); median age were 55.5 years (range, 18-70 years) in der(1;7) group; 52.5 years (range, 16-73 years) in -7/del(7q) group; 50.0 years (range, 16-73 years) in normal karyotype group. Male predominance was noted in both der(1;7) and -7/del(7q)

groups: male were 78 out of 94 (84.8%) in der(1;7) group; 72 out of 104 (69.2%) in -7/del(7q) group; 519 out of 858 (60.5%) in normal karyotype group. This tendency was also evident in der(1;7) group compared to -7/del(7q) group (P=.012).

As demonstrated in previous studies, MDS patients with der(1;7) were more likely to show a lower percentage of myeloblasts and slower disease progression than those with -7/del(7q) [12, 13]. In order to estimate the prognostic value of der(1;7) and -7/del(7q) in detail, we analyzed post-transplant outcomes by the disease status, and patients were divided into two groups; 655 (62.1%) at advanced status, and 399 (37.9%) at early disease status at transplantation. The demographic and baseline characteristics of patients are shown in Table 1.

Transplantation outcomes by disease-risk stratification

In the entire cohort, the 3-year probability of OS after allo-HSCT was 57.2% (95% CI 53.9-60.3); the 3-year CIR and TRM were 16.3% (95% CI 14.0-18.7%) and 27.0% (95% CI 24.3-29.9%), respectively. The univariate analysis demonstrated that patients with advanced disease status showed a worse OS (P<.001) and increased CIR (P<.001) than those with early disease status (Supplemental Figure 1A, B). However, no significant difference was observed in TRM by the disease status (Supplemental Figure 1C). Among

the patients with both advanced and early disease status, no significant difference was not observed for the cumulative incidences of neutrophil engraftment, acute-, and chronic-GVHD by each cytogenetic group (data not shown).

OS by the cytogenetic group in patients with advanced disease status

Among those with advanced disease status at allo-HSCT, 69, 75, and 511 patients had der(1;7), -7/del(7q), and normal karyotype, respectively (Supplemental Table 1).

The 3-year probabilities of OS after allo-HSCT were 50.4% (95% CI 37.4-62.0%), 36.2% (95% CI 24.7-47.8%), and 51.1% (95% CI 46.4-55.7%) in der(1;7), -7/del(7q), and normal karyotype groups, respectively (Figure 1A). In the univariate analysis using the log-rank test, OS was significantly shorter in -7/del(7q) group than in normal karyotype group (P=.011), whereas no significant difference was noted in OS between der(1;7) and normal karyotype groups (P=.780). In the multivariate analysis, -7/del(7q) group was a significantly worse factor than normal karyotype group (HR 1.38, 95% CI 1.00-1.89, P=.048), while der(1;7) group was not (HR 0.90, 95% CI 0.62-1.31, P=.583) (Table 2). There was no interaction modification between the cytogenetic group and other covariates. Four factors other than the cytogenetic group correlated with worse OS: recipient age (≥60 years, HR 1.39, 95% CI 1.05-1.85, P=.023), PS at transplantation (PS

1-4, HR 1.56, 95% CI 1.22-1.99, P<.001; missing data on PS, HR 1.87, 95% CI 1.26-2.77, P=.002), the type of donor source (unrelated cord blood, HR 1.85, 95% CI 1.33-2.56, P<.001), and the interval from diagnosis to transplantation (>7.8 months, HR 1.54, 95% CI 1.22-1.95, P<.001) (Supplemental Table 2).

CIR and TRM by the cytogenetic group in patients with advanced disease status

The 3-year CIR were 19.4% (95% CI 10.5-30.3%), 38.4% (95% CI 26.9-49.7%), and 20.7% (95% CI 17.1-24.5%) for der(1;7), -7/del(7q), and normal karyotype groups, respectively (Figure 1B). The univariate analysis using Gray test showed that the CIR was significantly higher for -7/del(7q) group than for normal karyotype group (P<.001), whereas no significant difference was noted between der(1;7) and normal karyotype groups (P=.816). Furthermore, -7/del(7q) group was likely to show a higher CIR than der(1;7) group in the Kaplan-Meier analysis (P=.015). The multivariate analysis demonstrated that CIR was significantly higher in -7/del(7q) group than in normal karyotype group (HR 2.11, 95% CI 1.36-3.280, P=.001) (see Table 2). There was no interaction modification between the cytogenetic group and other covariates. In the univariate and multivariate analyses, three factors were significant: PS at transplantation (PS 1-4, HR 2.32, 95% CI 1.38-3.90, P=.002), the use of anti-thymocyte globulin (ATG)

during conditioning (presence, HR 2.42, 95% CI 1.29-4.57, P=.006), and the type of donor source (unrelated bone marrow, HR 0.57, 95% CI 0.34-0.94, P=.028; unrelated cord blood, HR 1.58, 95% CI 1.01-2.51, P=.047) (see Supplemental Table 2). For the comparison between -7/del(7q) and der(1;7) groups, the higher CIR among -7/del(7q) group was maintained in the multivariate analysis (HR 2.19, 95% CI 1.08-4.44, P=0.029) (supplemental Table 3).

The 3-year TRM were 31.1% (95% CI 20.0-42.7%), 27.1% (95% CI 17.0-38.1%), and 29.1% (95% CI 25.0-33.3%) in the der(1;7), -7/del(7q), and normal karyotype groups, respectively (Figure 1C). The univariate and multivariate analyses did not identify the cytogenetic group as a significant factor for TRM. However, in the multivariate analysis, four factors correlated with higher TRM: recipient age at transplantation (≥60 year, HR 1.46, 95% CI 1.00-2.11, P=.045), the type of donor source (unrelated bone marrow, HR 1.72, 95% CI 1.11-2.66, P=.016; HLA-mismatched related graft, HR 3.02, 95% CI 1.73-5.24, P<.001; unrelated cord blood, HR 2.25, 95% CI 1.35-3.74, P=.002), the interval from diagnosis to transplantation (>7.8 months, HR 1.68, 95% CI 1.24-2.29, P=.001), and the year of transplantation (2004-2008, HR 0.62, 95% CI 0.41-0.94, P=.024; 2009-2012, HR 0.57, 95% CI 0.38-0.89, P=.013). The causes of death were shown in supplemental Table 4. No significant difference was observed among 3 groups.

OS by the cytogenetic group in patients with early disease status

Among patients with early disease status at transplantation, 23, 29, and 347 showed der(1;7), -7/del(7q), and normal karyotype, respectively (Supplemental Table 5).

The 3-year probabilities of OS after allo-HSCT were 47.3% (95% CI 21.5-69.5%), 70.5% (95% CI 49.3-84.1%), and 70.9% (95% CI 65.6-75.5%) in der(1;7), -7/del(7q), and normal karyotype groups, respectively (Figure 2A). The univariate and multivariate analyses revealed no significant differences in OS among three groups (Table 3). There was no interaction modification between the cytogenetic group and other covariates. In the multivariate analysis, recipient age at transplantation (≥60 years, HR 2.21, 95% CI 1.42-3.44, P<.001), the type of donor source (unrelated cord blood, HR 1.77, 95% CI 1.03-3.04, P=.037), and the type of disease-altering therapy prior to allo-HSCT (intensive chemotherapy, HR 2.10, 95% CI 1.15-3.84, P=.016) correlated with shorter OS (Supplemental Table 6).

Relapse and TRM by the cytogenetic group in patients with early disease status

The 3-year CIR were 9.5% (95% CI 1.5-26.8%), 13.8% (95% CI 4.2-29.0%), and 5.6% (95% CI 3.5-8.4%) in der(1;7), -7/del(7q), and normal karyotype groups, respectively

(Figure 2B). In terms of the cytogenetic group, the univariate and multivariate analyses showed no significant differences in CIR among three groups (see Table 3). Four factors other than the cytogenetic group correlated with a higher CIR: recipient age at transplantation (50-59 years, HR 3.08, 95% CI 1.05-9.10, P=.041), the intensity of the conditioning regimen (non-myeloablative conditioning regimen, HR 11.01, 95% CI 2.55-47.54, P=.001), the type of donor source (unrelated bone marrow, HR 0.28, 95% CI 0.10-0.77, P=.014), and the period of transplantation (2004-2008, HR 0.19, 95% CI 0.41-0.87, P=.033) (see Supplemental Table 4).

The 3-year TRM were 42.8% (95% CI 17.0-66.7%), 18.3% (95% CI 7.7-32.7%), and 23.3% (95% CI 18.8-28.0%) in der(1;7), -7/del(7q), and normal karyotype groups, respectively, without a significant difference (Figure 2C). The multivariate analysis demonstrated that the type of donor source (HLA-mismatched related graft, HR 2.44, 95% CI 1.01-5.88, P=.047; unrelated cord blood, HR 2.55, 95% CI 1.34-4.83, P=.004) and type of disease-altering therapy prior to allo-HSCT (intensive chemotherapy, HR 2.05, 95% CI 1.13-3.71, P=.018) had a significantly negative impact on TRM. There was no significant difference of causes of death among 3 groups (supplemental Table 7).

Discussion

The primary objective of this retrospective study was to evaluate the prognostic impact of the loss of chromosome 7q on the post-transplant outcomes of MDS patients. Previous studies analyzed the prognostic impact of the loss of 7q regardless of additional cytogenetic abnormalities [12-14]. To the best of our knowledge, the present study examined the largest number of post-transplant patients with der(1;7) or -7/del(7q) as the sole cytogenetic abnormality. Namely, the cohort of this study enabled a better estimation of the true prognostic impact of der(1;7) and -7/del(7q) on post-transplant outcomes.

The ratios of der(1;7) (n=94, 8.9%) and -7/del(7q) groups (n=104, 9.8%) to normal karyotype group (n=858, 81.3%) in our cohort were higher than those in the previous studies [28, 29]. Physician and patient willingness to consider the indication of allo-HSCT for these cytogenetic groups was reflected, at least in a part, the different distribution in our study. Another explanation for the different distribution was that der(1;7) was more frequent in Japanese than Caucasians as previously reported [29].

One of the main questions in the present study was the prognostic impact of der(1;7) after allo-HSCT. In the original IPSS [2], the loss of 7q was assigned as a poor prognosis factor, and der(1;7) was considered to be a more unfavorable indicator than normal karyotype. This resulted in the selection of aggressive therapeutic strategies for der(1;7)(q10;p10) group, including disease-altering treatments (i.e. DNA

hypomethylating agents, intensive chemotherapy, and allo-HSCT) [13]. However, it currently remains unclear whether der(1;7) exhibits a survival disadvantage over normal karyotype due to the lack of any direct comparisons between der(1;7) and normal karyotype in MDS patients. It is important to note that we did not observe any differences in post-transplant outcomes between der(1;7) and normal karyotype groups with early and advanced disease status. One possible interpretation of these results is that der(1;7) did not have a prognostic impact in MDS patients after allo-HSCT.

Another interesting result of the present study was that der(1;7) group showed a lower CIR than -7/del(7q) group among the patients with advanced disease status, suggesting that der(1;7) group would benefit from allo-HSCT more than -7/del(7q) groups. The recent studies revealed that MDS patients with der(1;7) had the distinct clinical and pathological features, including ethnical differences and mutation profile [29, 30]. However, it is controversial whether der(1;7) abnormality defines a separate prognostic group in the previous studies involved both transplant and non-transplant patients [12, 13, 31]. In terms of prognostic value of der(1;7) group, our findings provided the clearer insights into clinical outcomes in MDS patients with der(1;7) who undergo allo-HSCT.

The important result was that the impact of -7/del(7q) differed by disease status; it correlated with worse OS and higher CIR with advanced disease status, but not early

disease status. In other words, -7/del(7q) exhibited different influences on post-transplant outcomes by the trajectory of the bone marrow blast percentage from the initial diagnosis to the time of transplantation. Since MDS patients with -7/del(7q) were more likely to progress to advanced disease status [12], a bridging strategy using DNA hypomethylating agents and/or chemotherapy prior to allo-HSCT is warranted for these patients [32-34]. In this regard, the detection of somatic mutations related to disease progression may be useful for making better decisions on how to treat the -7/del(7q) group [35].

Among patients with advanced disease status, CIR was significantly higher in -7/del(7q) group than in normal karyotype group. This may have been partly due to the larger burden of residual tumor cells after allo-HSCT in -7/del(7q) group than in normal karyotype group. Thus, the monitoring of minimal residual disease may be helpful for -7/del(7q) using novel molecular-based approaches (e.g. a digital polymerase chain reaction [PCR] method and next-generation sequencing), multiparameter flow cytometry, and WT1 expression levels with PCR [36-38]. These approaches may help to employ and optimize post-transplant therapy, such as the introduction of DNA hypomethylating agents, other compounds, and donor lymphocyte infusion as pre-emptive strategies to prevent the future relapse of MDS [39-45].

It was interesting to note that conditioning regimen-related factors correlated with

increased CIR. The use of ATG in the conditioning regime for patients with advanced disease status and non-myeloablative conditioning regimen for those with early disease status were significant factors for a significantly higher CIR and were independent from the cytogenetic group. Previous studies indicated that the graft-versus-leukemia effect and optimal intensity of the conditioning regimen were crucial for the long-term survival of MDS patients [24, 46-50]. These findings suggested that careful attention to the conditioning regimen in consideration of the disease status at transplantation is needed for patients with single der(1;7) or -7/del(7q) abnormality and normal karyotype.

We were unable to assess the impact of somatic mutations due to the lack of data in TRUMP. Previous studies showed that the distinct mutation spectrum was identified in each karyotype; MDS patients with der(1;7) more often had *RUNX1* gene mutations [12, 30], whereas those with -7/del(7q) did the mutations in *SAMD9*, *SAMD9L*, *EZH2*, *MLL3*, and *TP53* genes [51, 52]. Based on the presence of mutations in several genes, such as *RUNX1* and *TP53* genes, negatively affecting post-transplant outcomes [53, 54], further attempts to integrate cytogenetics, molecular genetics, and pathological data are crucial to generate better prognostic system for pre-transplant candidates with the loss of chromosome 7q. In addition, the sequencing-based monitoring for measurable residual disease was reported to be helpful for predicting disease progression following allo-HSCT

[55], which could support the decision to promptly initiate preemptive and salvage treatment. For MDS patients with der(1;7) or -7/del(7q) abnormality, it would be crucial to develop the optimal diagnostic modality using cytogenetic analysis in combination with sequencing-based monitoring, on the basis sensitivity and accessibility.

There were several limitations in the present study. We were unable to evaluate the impact of IPSS, revised IPSS, and karyotype, including additional cytogenetic abnormalities, before allo-HSCT on post-transplant outcome [56-58]. Considering these predictive values for post-transplant outcomes, it would be of interest to determine whether these factors are helpful for risk-stratification among der(1;7) or -7/del(7q) groups. Furthermore, we carefully assessed the eligibility of patients who met all inclusion and exclusion criteria; however, patient characteristics and transplant procedures were heterogeneous. These factors may have exerted a bias and potentially affected the results obtained. Therefore, these results need to be cautiously interpreted and confirmed in larger prospective studies.

In conclusion, the present study showed that allo-HSCT may provide durable remission for MDS patients with the loss of chromosome 7q, whereas its impact on OS and CIR after transplantation may differ based on the type of loss of 7q. The present results may contribute to improving the management of MDS patients with the loss of chromosome

7q before and after transplantation.

Authorship

Contributions

H.I. and Y.M. designed the research, organized the project, analyzed the data, and wrote the manuscript. H.I., K.A., J.A., T. Ishikawa, K. Ishiyama, and Y.M. collected data from TRUMP. H.I., K.A., J.A., T. Ishikawa, K. Ishiyama, N.U., T.F., Y. Ozawa, S.O., N.U., T.E., K. Iwato, Y. Ohno, M.T., T. Ichinohe, Y.A., and Y.M. interpreted data and reviewed and approved the final manuscript.

Conflict of interest

The authors state that they have no conflict of interest.

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Appendix

The following institutions and hematologists contributed to this study: Nagasaki University: Dr. H. Itonaga and Dr. Y. Miyazaki; Kyoto University: Dr. A. Takeda and Dr. K. Aoki; Kanagawa Cancer Center: Dr. J. Aoki, Dr. M. Tanaka, and Dr. T Takahana; Kanazawa University Hospital: Dr. K. Ishiyama; Kobe City Medical General Hospital: Dr. Y. Shimomura and Dr. T. Ishikawa; Keio University School of Medicine: Drs. J. Kato and S. Okamoto; Japanese Red Cross Nagoya First Hospital: Dr. Y. Ozawa; Tokyo Metropolitan Cancer and Infectious Disease Centre Komagome Hospital: Drs. K. Kakizoe and N. Doki; JA Aichi Konan Kosei Hospital: Dr. A. Kohno; Toranomon Hospital: Dr. S. Takagi; Aichi Medical University: Dr. A. Takami; Hyogo College of Medicine: Dr. H. Tamaki; Akita University Hospital: Dr. M. Hirokawa; Mishuku Hospital: Dr. K. Masuoka; Niigata University: Dr. M. Masuko; Kinki University: Dr. K. Ashizawa and Dr. T. Ashida; NTT Medical Center Tokyo: Dr. R. Kida and Dr. K. Usuki; Hamanomachi Hospital: Dr. T. Eto; Sapporo Hokuyu Hospital: Dr. K. Minauchi and Dr. S. Ohta; Tohoku University Hospital: Dr. Y. Onishi; Kanazawa University Graduate

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Figure Legends

Figure 1. Post-transplant outcomes of MDS with advanced disease status

(A) Overall survival (OS) after allo-HSCT. (B) Cumulative incidence of relapse (CIR).

(C) Cumulative incidence of transplant-related mortality (TRM).

Figure 2. Post-transplant outcomes of MDS with early disease status

(A) OS. (B) CIR. (C) TRM.

Table 1. Patient characteristics

	Advanced disease status	Early disease status	P
Total	655	399	
Median age at allo-HSCT (range), y	51 (16 - 73)	44 (16 - 72)	<.001
Age at allo-HSCT			<.001
≤ 49	251	243	
50-59	214	93	
≥ 60	190	63	
Gender			.025
Male	433	236	
Female	222	163	
Sex match			
match	349	203	
mismatch	282	188	
missing	24	8	
Karyotype			.001
der(1;7)	69	23	
-7/del(7q)	75	29	
Normal karyotype	511	347	
FAB at diagnosis			<.001
RA	84	386	
RARS	5	13	
RAEB	434	-	
RAEB-t	132	-	
IPSS at diagnosis			
Low	29	33	
Intermediate-1	136	170	
Intermediate-2	197	21	
High	78	1	
Missing	215	174	
Performance status at allo-HSCT			
0	306	175	
1-4	297	202	
Missing	52	22	
Bone marrow blasts at allo-HSCT			<.001
<5%	85	299	
≥5%	570	-	
Conditioning regimen intensity			.932
Myeloablative	392	243	
Reduced intensity	231	138	
Non-myeloablative	32	18	
Donor source			<.001
HLA-matched related	163	123	
HLA-mismatched related	40	20	
Unrelated bone marrow	284	198	
Unrelated cord blood	168	58	
GVHD prophylaxis			
CsA-based	300	181	
Tac-based	345	212	
Other than calcineurin inhibitor-based	7	6	
Missing	3	0	
Antithymocyte globulin			.085
No	608	358	
Yes	47	41	
Year of allo-HSCT			.008
1999-2003	131	92	
2004-2008	194	145	
2009-2012	330	162	
Interval between diagnosis and allo-HSCT, mo		17.5 (0.5 - 394.6)	<.001
Disease-altering therapy prior to allo-HSCT			<.001
Intensive chemotherapy alone	253	20	
Azacitidine treatment alone	38	7	
Intensive chemotherapy and azacitidine treatment	11	3	
No treatment with disease-altering therapy	353	369	
Follow-up of survivors, y	3.1 (0.1 - 14.4)	4.3 (0.1 - 13.3)	
Final status			
Alive	333	275	
Death after relapse (disease-associated death)	134	26	
Death without relapse (transplant-related death)	188	98	

Abbreviations: der(1;7) indicates, 46, XY (or 46, XX), +1, der(1;7)(q10;p10); -7/del(7q), monosomy 7 or the partial deletion of 7q; FAB classification, French-American-British classification; RA, refractory anemia; RARS, RA with ringed

sideroblasts; RAEB, RA with excess blasts; RAEB-t, RAEB in transformation; allo-HSCT, allogeneic hematopoietic stem cell transplantation; HLA, human leukocyte antigen; CsA, cyclosporine A; Tac, tacrolimus.

Table 2. Impact of the cytogenetic group in patients with advanced disease status

Outcomes Cytogenetic group	Univariate analysis		Multivariate analysis	
	HR (95% CI)	***P***	**HR (95% CI)**	***P***
Overall mortality*				
Normal karyotype	1.00		1.00	
der(1;7)	1.05 (0.73-1.52)	0.781	0.90 (0.62-1.31)	0.583
-7/del(7q)	1.49 (1.09-2.04)	0.012	1.38 (1.00-1.89)	0.048
Transplant-related mortality†				
Normal karyotype	1.00		-	-
der(1;7)	1.08 (0.69-1.70)	0.736	-	-
-7/del(7q)	0.95 (0.60-1.51)	0.840	-	-
Relapse ‡				
Normal karyotype	1.00		1.00	
der(1;7)	0.93 (0.51-1.70)	0.808	0.90 (0.47-1.72)	0.757
-7/del(7q)	2.15 (1.39-3.30)	0.001	2.11 (1.36-3.28)	0.001

The multivariate analysis including the cytogenetic group as a covariate identified other significant factors as follows:

*Other factors associated with worse OS were recipient age at transplantation (≥60 year), performance status (PS) at transplantation (PS 1-4 and missing data), the type of donor source (unrelated cord blood), and the interval from diagnosis to transplantation (>7.8 months).

†Other factors associated with worse TRM were recipient age at transplantation (≥60 year), the type of donor source (HLA-mismatched related graft, unrelated bone marrow, and unrelated cord blood), and the interval from diagnosis to transplantation (>7.8 months); another factor associated with better TRM was the period of transplantation (2004-2008 and 2009-2012).

‡Other factors associated with an increased relapse rate were PS at transplantation (PS 1-4), the use of ATG in the conditioning regimen (presence), the type of GVHD prophylaxis (other than calcineurin inhibitor-based), and type of donor source (unrelated cord blood); another factor associated with a reduced relapse rate was the type of donor source (unrelated bone marrow).

Abbreviations: HR, hazard ratio; CI, confidential interval.

Table 3. Impact of the cytogenetic group in patients with early disease status

Outcomes Cytogenetic group	Univariate analysis HR (95% CI)	*P*
Overall mortality*		
Normal karyotype	1.00	
der(1;7)	1.44 (0.73-2.85)	0.294
-7/del(7q)	0.99 (0.50-1.95)	0.968
Transplant-related mortality†		
Normal karyotype	1.00	
der(1;7)	1.35 (0.65-2.79)	0.421
-7/del(7q)	0.81 (0.36-1.86)	0.624
Relapse‡		
Normal karyotype	1.00	
der(1;7)	1.56 (0.38-6.49)	0.537
-7/del(7q)	2.47 (0.87-7.02)	0.091

The multivariate analysis including the cytogenetic group as a covariate identified other significant factors as follows:

*Other factors associated with worse OS were recipient age at transplantation (≥60 year), the type of donor source (unrelated cord blood), and the type of disease-altering therapy prior to allo-HSCT (intensive chemotherapy alone).

†Other factors associated with worse TRM were the type of donor source (HLA-mismatched related graft and unrelated cord blood) and type of disease-altering therapy prior to allo-HSCT (intensive chemotherapy alone).

‡Other factors associated with an increased relapse rate were recipient age at transplantation (50-59 years) and the intensity of the conditioning regimen (non-myeloablative conditioning regimen); other factors associated with a reduced relapse rate were the type of donor source (HLA-mismatched related graft and unrelated bone marrow) and period of transplantation (2004-2008).

Figure 1. Post-transplant outcomes of MDS with advanced disease status at transplantation

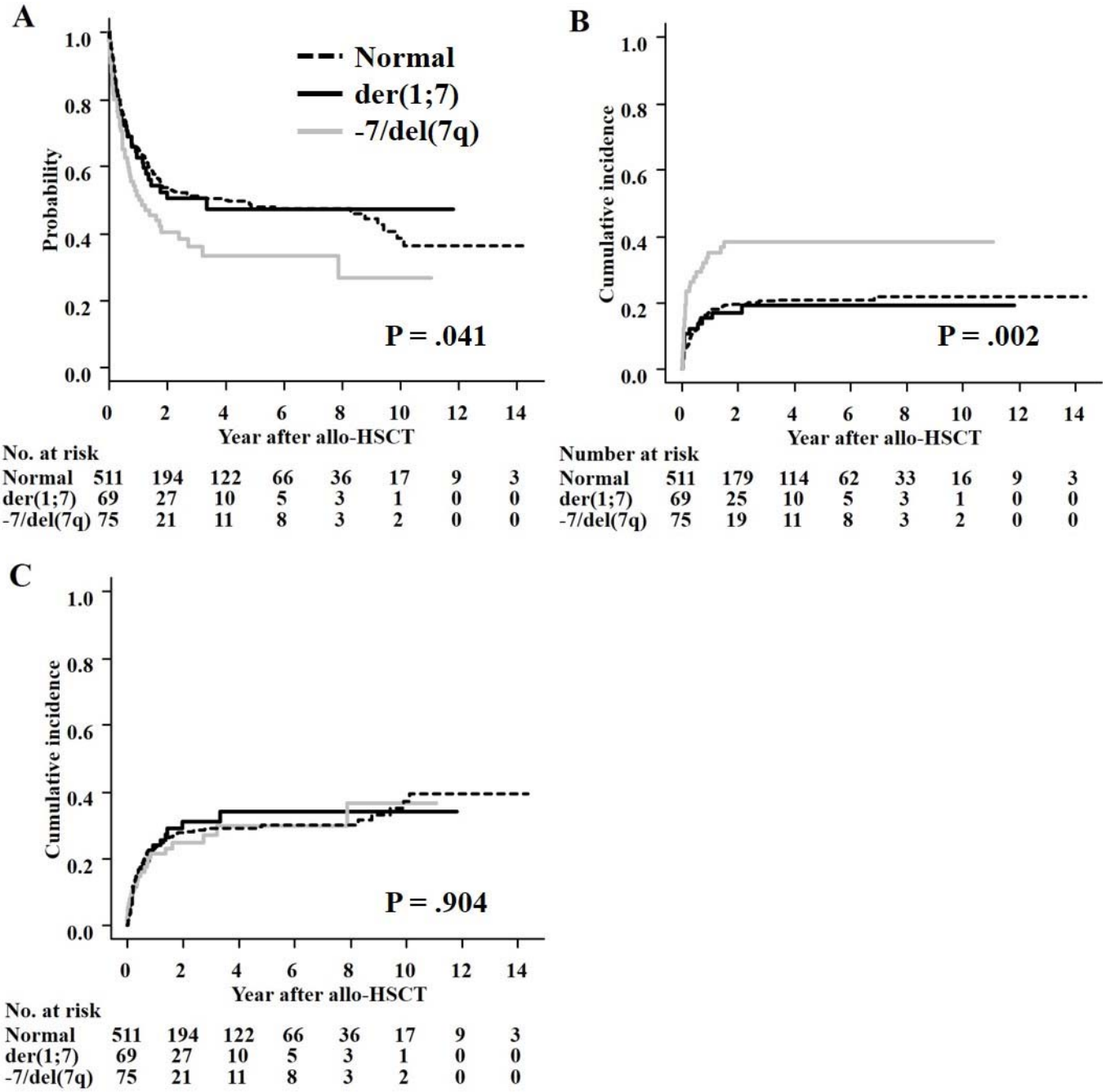
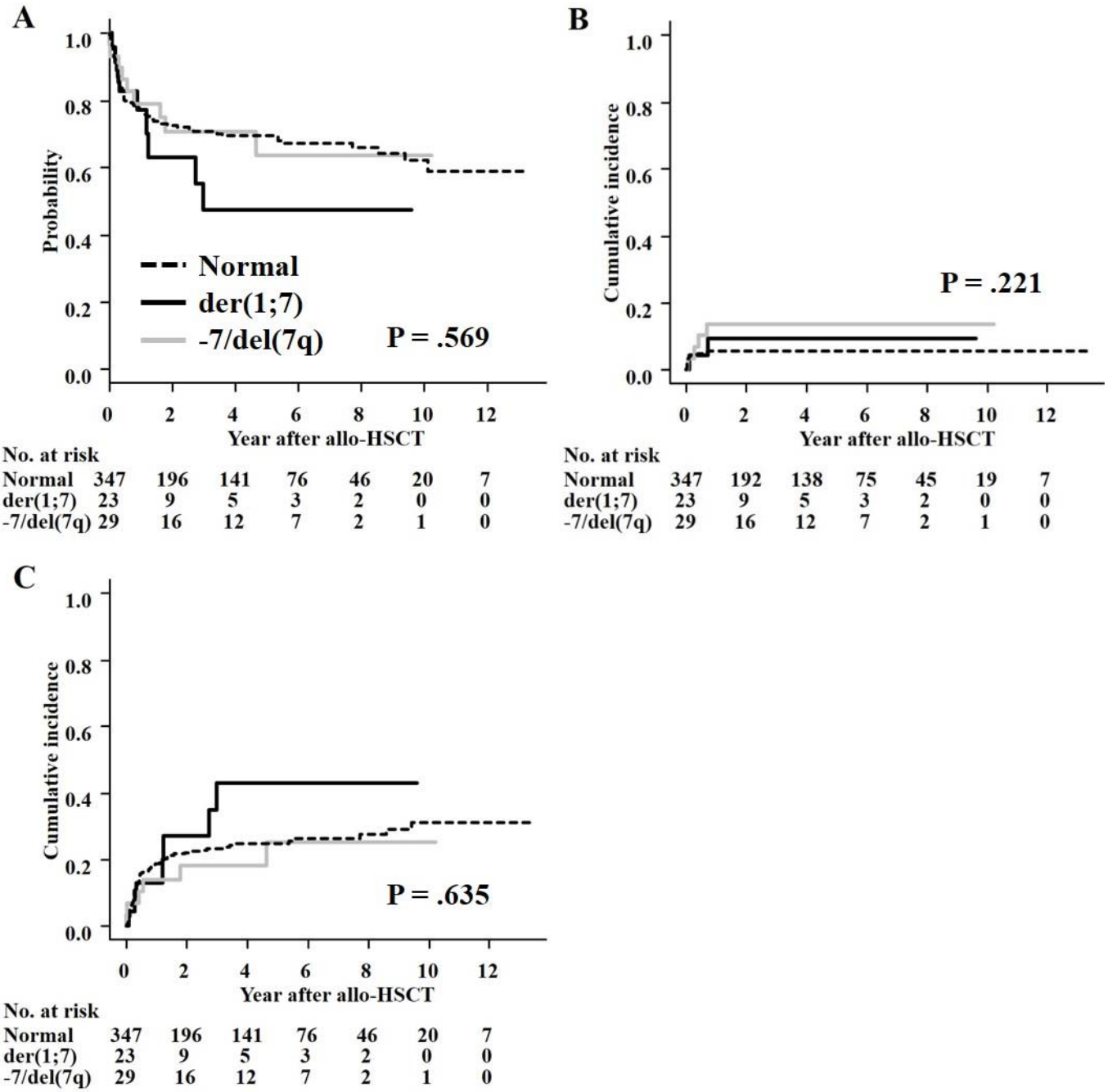


Figure 2. Post-transplant outcomes of MDS with early disease status at transplantation



Supplemental Table 1. Characteristics of patients with advanced disease status

	der(1;7)	Total -7/del(7q)	Normal	*P*
Total	69	75	511	
Median age at allo-HSCT (range), y	58 (19-73)	53 (16-73)	54 (16-73)	0.005
Age at allo-HSCT				0.019
≤ 49	15	33	203	
50-59	24	22	168	
≥ 60	30	20	140	
Gender				0.002
Male	58	53	322	
Female	11	22	189	
Sex match				0.358
match	39	33	277	
mismatch	28	37	217	
missing	2	5	17	
FAB at diagnosis				0.074
RA	16	7	61	
RARS	0	1	4	
RAEB	43	56	335	
RAEB-t	10	11	111	
IPSS at diagnosis				<0.001
Low	2	1	26	
Int-1	11	5	120	
Int-2	30	25	142	
High	15	19	44	
Missing	11	25	179	
Performance status at allo-HSCT				0.143
0	32	25	249	
1-4	33	43	221	
Missing	4	7	41	
Bone marrow blasts at allo-HSCT				<0.001
<5%	3	2	80	
≥5%	66	73	431	
Intensity of the conditioning regimen				0.256
Myeloablative	35	40	317	
Reduced intensity	30	32	169	
Non-myeloablative	4	3	25	
Donor source				0.621
HLA-matched related	17	15	131	
HLA-mismatched related	6	7	27	
Unrelated bone marrow	26	33	225	
Unrelated cord blood	20	20	128	
GVHD prophylaxis				0.625
CsA-based	34	38	228	
Tac-based	33	35	277	
Other	1	1	5	
Missing	1	1	1	
Use of ATG in the conditioning regimen				0.601
No	66	70	472	
Yes	3	5	39	
Year of allo-HSCT				0.224
1999-2003	8	15	108	
2004-2008	18	25	151	
2009-2012	43	35	252	
Interval between diagnosis and allo-HSCT, mo	9.4 (1.1-82.2)	7.3 (1.6-75.9)	7.8 (0.7-237.8)	0.402
Disease-altering therapy prior to allo-HSCT				0.154
ICT alone	22	23	208	
Azacitidine treatment alone	1	5	32	
ICT and azacitidine treatment	2	1	8	
No treatment with disease-altering therapy	44	46	263	
Follow-up of survivors, y	2.6 (0.3-11.8)	2.8 (0.3-11.1)	3.2 (0.1-14.4)	0.830
Final status				
Alive	36	28	269	

Death after relapse (disease-associated death)	12	26	96
Death without relapse (treatment-related death)	21	21	146

Abbreviations: der(1;7) indicates, 46, XY (or 46, XX), +1, der(1;7)(q10;p10); -7/del(7q), monosomy 7 or the partial deletion of 7q; FAB classification, French-American-British classification; RA, refractory anemia; RARS, RA with ringed sideroblasts; RAEB, RA with excess blasts; RAEB-t, RAEB in transformation; allo-HSCT, allogeneic hematopoietic stem cell transplantation; HLA, human leukocyte antigen; CsA, cyclosporine A; Tac, tacrolimus; ICT, intensive chemotherapy.

Supplemental Table 2. Prognostic factors analyzed in patients with advanced disease status

Variable	Overall mortality				Treatment-related mortality				Relapse			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Patient sex												
Female	1.00		1.00		1.00		-	-	1.00		-	-
Male	1.40 (1.11-1.78)	0.005	1.26 (0.98-1.61)	0.068	1.30 (0.95-1.77)	0.102	-	-	1.19 (0.83-1.71)	0.341	-	-
Sex matching												
Match	1.00		-	-	1.00		-	-	1.00		-	-
Mismatch	0.92 (0.73-1.15)	0.465	-	-	1.05 (0.78-1.41)	0.732	-	-	0.76 (0.53-1.08)	0.127	-	-
Age at transplantation												
49 years or younger	1.00		1.00		1.00		1.00		1.00		not selected	
50-59 years	1.25 (0.95-1.63)	0.106	1.15 (0.88-1.51)	0.315	1.04 (0.73-1.48)	0.827	0.98 (0.70-1.42)	0.981	1.49 (0.99-2.23)	0.054	not selected	
Older than 59 years	1.74 (1.33-2.28)	<0.001	1.39 (1.05-1.85)	0.023	1.43 (1.01-2.03)	0.042	1.46 (1.00-2.11)	0.045	1.46 (0.96-2.23)	0.077	not selected	
Performance status at allo-HSCT												
0	1.00		1.00		1.00		1.00		1.00		1.00	
1-4	1.64 (1.29-2.07)	<0.001	1.56 (1.22-1.99)	<0.001	1.35 (0.99-1.83)	0.057	1.33 (0.97-1.82)	0.073	3.20 (1.96-5.23)	<0.001	2.51 (1.52-4.13)	<0.001
Missing	1.88 (1.29-2.73)	0.001	1.87 (1.26-2.77)	0.002	2.11 (1.32-3.35)	0.002	1.55 (0.90-2.68)	0.108	0.67 (0.32-1.42)	0.297	0.65 (0.30-1.38)	0.259
Blasts in bone marrow at allo-HSCT												
Lower than 5%			1.00		-	-	-	-	-	-	-	-
5% or higher	1.83 (1.25-2.67)	0.002	1.40 (0.94-2.10)	0.099	1.47 (0.91-2.36)	0.112	-	-	1.58 (0.91-2.75)	0.107	-	-
Conditioning regimen												
MAC	1.00		not selected		1.00		-	-	1.00		not selected	
RIC	1.31 (1.04-1.65)	0.023	not selected		1.03 (0.76-1.39)	0.850	-	-	1.64 (1.16-2.33)	0.005	not selected	
NMAC	1.73 (1.12-2.68)	0.013	not selected		0.80 (0.40-1.63)	0.543	-	-	2.77 (1.44-5.32)	0.002	not selected	
GVHD prophylaxis												
Cyclosporine-based	1.00		-	-	1.00		-	-	1.00		1.00	
Tacrolimus-based	1.09 (0.87-1.36)	0.458	-	-	1.11 (0.83-1.48)	0.476	-	-	0.96 (0.68-1.34)	0.796	1.00 (0.67-1.49)	0.982
Other	1.17 (0.43-3.17)	0.753	-	-	not calculated		-	-	3.39 (1.26-9.09)	0.015	4.50 (1.81-11.19)	0.001
Type of donor												
HLA-matched related donor	1.00		1.00		1.00		1.00		1.00		1.00	
HLA-mismatched related donor	1.76 (1.11-2.81)	0.017	1.55 (0.96-2.51)	0.074	2.70 (1.53-4.76)	0.001	3.02 (1.73-5.24)	<0.001	0.64 (0.27-1.50)	0.305	0.41 (0.16-1.04)	0.062
Unrelated bone marrow donor	1.26 (0.94-1.70)	0.120	0.95 (0.69-1.30)	0.752	1.96 (1.31-2.92)	0.001	1.72 (1.11-2.66)	0.016	0.59 (0.37-0.92)	0.020	0.57 (0.34-0.94)	0.028
Unrelated cord blood donor	2.35 (1.72-3.19)	<0.001	1.85 (1.33-2.56)	<0.001	2.24 (1.45-3.47)	<0.001	2.25 (1.35-3.74)	0.002	1.64 (1.08-2.49)	0.020	1.58 (1.01-2.51)	0.047
Period of transplantation												
1999-2003	1.00		-	-	1.00		1.00		1.00		not selected	
2004-2008	0.91 (0.68-1.22)	0.529	-	-	0.71 (0.49-1.04)	0.075	0.62 (0.41-0.94)	0.024	1.58 (0.96-2.58)	0.072	not selected	
2009-2012	0.79 (0.60-1.05)	0.105	-	-	0.69 (0.49-0.97)	0.031	0.57 (0.38-0.89)	0.013	1.24 (0.77-2.01)	0.379	not selected	
Interval from diagnosis to allo-HSCT*												
7.8 months or shorter	1.00		-	-	1.00		1.00	-	1.00		-	-
Longer than 7.8 months	1.50 (1.20-1.87)	<0.001	1.54 (1.22-1.95)	<0.001	1.79 (1.33-2.41)	<0.001	1.68 (1.24-2.29)	0.001	0.90 (0.64-1.27)	0.556	-	-
Use of ATG in the conditioning regimen												
No	1.00		not selected		1.00		-	-	1.00		-	-
Yes	1.46 (0.99-2.16)	0.054	not selected		0.85 (0.45-1.59)	0.612	-	-	1.85 (1.08-3.14)	0.024	2.42 (1.29-4.57)	0.006
Disease-altering therapy prior to allo-HSCT												
No treatment with disease-altering therapy	1.00		-	-	1.00		-	-	1.00		-	-
ICT alone	1.05 (0.83 - 1.31)	0.690	-	-	0.97 (0.72 - 1.30)	0.819	-	-	1.11 (0.79 - 1.57)	0.555	-	-
Azacitidine treatment alone	0.75 (0.40 - 1.38)	0.348	-	-	0.72 (0.34 - 1.54)	0.401	-	-	0.84 (0.37 - 1.93)	0.681	-	-
ICT and azacitidine treatment	1.87 (0.83 - 4.24)	0.133	-	-	2.15 (0.92 - 5.04)	0.077	-	-	0.45 (0.59 - 3.49)	0.447	-	-

*The median interval from the diagnosis to allo-HSCT was 7.8 months in MDS patients with advanced disease status.

Supplemental Table 3. Prognostic factors analyzed in patients having der(1;7) or -7/del(7q) with advanced disease status

	Overall survival				Treatment-related mortality				Relapse			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
Variable	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Karyotype at diagnosis												
der(1;7)	1.00		-	-	1.00		-	-	1.00		1.00	
-7/del(7q)	1.42 (0.91-2.22)	0.120	-	-	0.88 (0.48-1.61)	0.682	-	-	2.28 (1.15-4.51)	0.018	2.19 (1.08-4.44)	0.029
Patient sex												
Female	1.00		-	-	1.00		-	-	1.00		1.00	
Male	1.51 (0.87-2.62)	0.139	-	-	0.77 (0.40-1.47)	0.425	-	-	3.24 (1.20-8.72)	0.020	4.23 (1.48-12.04)	0.007
Sex matching												
Match	1.00		-	-	1.00		-	-	1.00		-	-
Mismatch	0.98 (0.62-1.55)	0.938	-	-	0.73 (0.39-1.37)	0.327	-	-	1.11 (0.57-2.14)	0.766	-	-
Age at transplantation												
49 years or younger	1.00		-	-	1.00		-	-	1.00		*not selected*	
50-59 years	1.24 (0.72-2.16)	0.439	-	-	0.94 (0.47-1.89)	0.866	-	-	1.91 (0.76-4.80)	0.166	*not selected*	
Older than 59 years	1.32 (0.77-2.27)	0.315	-	-	0.61 (0.28-1.32)	0.214	-	-	2.96 (1.24-7.07)	0.015	*not selected*	
Performance status at allo-HSCT												
0	1.00		*not selected*		1.00		1.00		1.00		1.00	
1-4	1.87 (1.03-3.42)	0.041	*not selected*		0.33 (0.09-1.28)	0.110	0.26 (0.06-1.07)	0.063	3.93 (1.88-8.24)	<0.001	2.93 (1.35-6.35)	0.007
Missing	1.56 (0.71-3.42)	0.270	*not selected*		2.35 (0.86-6.44)	0.095	2.41 (0.89-6.57)	0.084	*not calculated*		*not calculated*	
Blast in bone marrow at allo-HSCT												
Lower than 5%	1.00		-	-	1.00		-	-	1.00		-	-
5% or higher	1.86 (0.46-7.57)	0.387	-	-	1.66 (0.24-11.40)	0.604	-	-	0.78 (0.23-2.62)	0.685	-	-
Conditioning regimen												
MAC	1.00		-	-	1.00		-	-	1.00		-	-
RIC	1.03 (0.66-1.63)	0.882	-	-	0.85 (0.46-1.58)	0.613	-	-	1.31 (0.70-2.45)	0.406	-	-
NMAC	1.14 (0.41-3.19)	0.802	-	-	0.89 (0.21-3.73)	0.876	-	-	0.64 (0.07-5.71)	0.691	-	-
GVHD prophylaxis												
Cyclosporine-based	1.00		-	-	1.00		-	-	1.00		-	-
Tacrolimus-based	1.00 (0.64-1.57)	0.998	-	-	0.87 (0.47-1.60)	0.646	-	-	1.20 (0.63-2.28)	0.582	1.27 (0.63-2.56)	0.502
Other	1.73 (0.42-7.18)	0.451	-	-	not calculated		-	-	4.65 (2.62-8.25)	<0.001	9.03 (3.61-22.58)	<0.001
Type of donor												
HLA-matched related donor	1.00		1.00		1.00		*not selected*		1.00		1.00	
HLA-mismatched related donor	1.65 (0.66-4.14)	0.286	1.60 (0.64-4.02)	0.319	2.97 (0.97-9.09)	0.056	*not selected*		0.63 (0.13-3.02)	0.562	0.59 (0.12-2.86)	0.509
Unrelated bone marrow donor	1.53 (0.80-2.93)	0.201	1.49 (0.77-2.86)	0.234	2.80 (1.10-7.13)	0.031	*not selected*		0.61 (0.23-1.62)	0.324	0.73 (0.24-2.16)	0.564
Unrelated cord blood donor	3.24 (1.68-6.25)	<0.001	3.17 (1.64-6.11)	0.001	2.05 (0.74-5.68)	0.166	*not selected*		2.83 (1.20-6.67)	0.018	2.76 (1.06-7.20)	0.037
Period of transplantation												
1999-2003	1.00		-		1.00		*not selected*		1.00		-	-
2004-2008	0.83 (0.46-1.51)	0.541	-		0.49 (0.22-1.07)	0.075	*not selected*		2.40 (0.67-8.60)	0.178	-	-
2009-2012	0.62 (0.35-1.11)	0.35	-		0.47 (0.23-0.95)	0.035	*not selected*		2.14 (0.62-7.40)	0.230	-	-
Interval from diagnosis to allo-HSCT												
7.8 months or shorter	1.00		-		1.00		1.00		1.00		1.00	
Longer than 7.8 months	1.28 (0.82-2.00)	0.268	-		2.32 (1.21-4.46)	0.012	2.30 (1.17-4.54)	0.016	0.55 (0.29-1.06)	0.073	0.53 (0.25-1.10)	0.250
Aanti-thymocyte globuline as conditioning												
No	1.00		1.00		1.00		1.00		1.00		-	-
Yes	2.16 (0.94-4.98)	0.071	2.03 (0.88-4.71)	0.096	2.73 (0.91-8.17)	0.072	3.59 (1.41-9.14)	0.007	0.51 (0.06-4.11)	0.530	-	-

Supplemental Table 4. Causes of death among patients with advanced disease status

	No. of patients (%)					
	der(1;7)		-7/del(7q)		Normal	
Recurrence of MDS	12	(35.3)	26	(55.3)	96	(39.8)
Graft failure/rejection	0	(0.0)	0	(0.0)	6	(2.5)
GVHD	3	(8.8)	7	(14.9)	21	(8.7)
Infection	7	(20.6)	7	(14.9)	44	(18.3)
Idiopathic pneumonia	2	(5.9)	2	(4.3)	13	(5.4)
Organ failure	3	(8.8)	3	(6.4)	26	(10.8)
Secondary cancer	0	(0.0)	0	(0.0)	3	(1.2)
Bleeding	1	(2.9)	1	(2.1)	12	(5.0)
TMA	0	(0.0)	0	(0.0)	4	(1.7)
SOS	1	(2.9)	0	(0.0)	8	(3.3)
Other	5	(14.7)	1	(2.1)	8	(3.3)
Total	34	(100.0)	47	(100.0)	241	(100.0)

Abbreviations: MDS, myelodysplastic syndrome; TMA, thrombotic microangiopathy; SOS, sinusoid obstruction syndrome.

Supplemental Table 5. Characteristics of patients with early disease status

	Total			
	der(1;7)	-7/del(7q)	Normal	*P*
Total	23	29	347	
Median age at allo-HSCT (range), y	48 (18-66)	51 (16-69)	43 (16-72)	0.045
Age at allo-HSCT				0.234
<49	12	13	218	
50-59	8	10	75	
≥60	3	6	54	
Gender				0.013
Male	20	19	197	
Female	3	10	150	
Sex match				0.59
match	13	11	179	
mismatch	10	17	161	
missing	0	1	7	
FAB at diagnosis				0.663
RA	23	28	335	
RARS	0	1	12	
RAEB	-	-	-	
RAEB-t	-	-	-	
IPSS at diagnosis				<0.001
Low	1	2	30	
Int-1	5	0	165	
Int-2	9	10	2	
High	0	0	1	
Missing	8	17	149	
Performance status at allo-HSCT				0.898
0	11	14	150	
1-4	12	14	176	
Missing	0	1	21	
Intensity of the conditioning regimen				0.334
Myeloablative	13	16	214	
Reduced intensity	10	13	115	
Non-myeloablative	0	0	18	
Donor source				0.254
HLA-matched related	7	14	102	
HLA-mismatched related	1	2	17	
Unrelated bone marrow	10	8	180	
Unrelated cord blood	5	5	48	
GVHD prophylaxis				0.65
CsA-based	10	14	157	
Tac-based	12	14	186	
Other	1	1	4	
Use of ATG in the conditioning regimen				0.096
No	23	28	307	
Yes	0	1	40	
Year of allo-SCT				0.159
1999-2003	1	8	83	
2004-2008	12	12	121	
2009-2012	10	9	143	
Interval between diagnosis and allo-HSCT, mo	10.1 (0.5-133.2)	18.9 (2.2-119.9)	19.7 (0.5-394.6)	0.019
Disease-altering therapy prior to SCT				0.152
Intensive chemotherapy alone	1	1	18	
Azacitidine treatment alone	1	2	4	
Intensive chemotherapy and azacitidine treatment	0	1	2	
No treatment with disease-altering therapy	21	25	323	
Follow-up of survivors, y	1.8 (0.3-9.6)	4.4 (0.5-10.2)	4.4 (0.1-13.3)	0.199
Final status				
Alive	14	20	241	
Death after relapse (disease-associated death)	2	3	21	
Death without relapse (treatment-related death)	7	6	85	

Supplemental Table 6. Prognostic factors analyzed in patients with early disease status

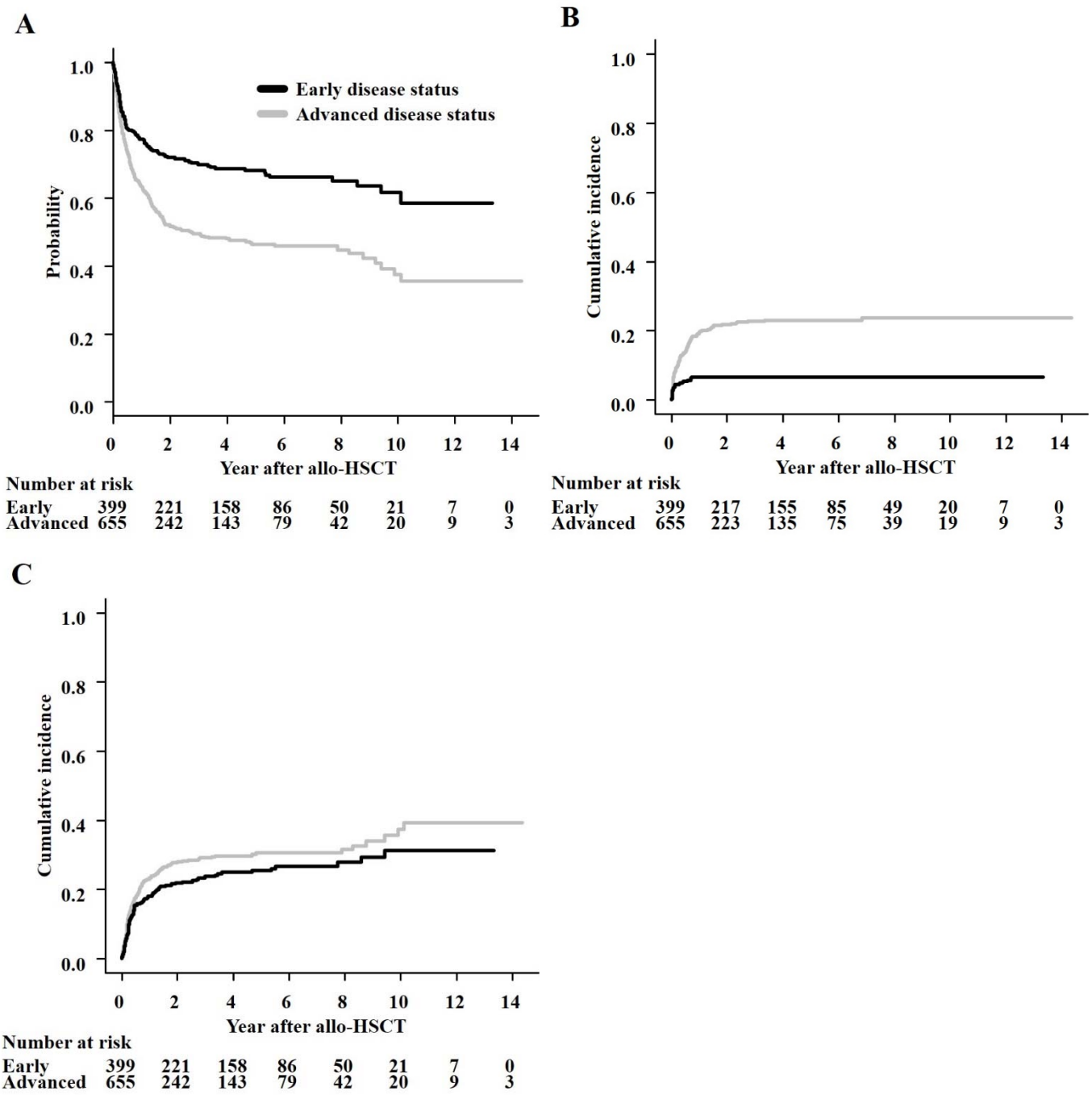
Variable	Overall mortality				Treatment-related mortality				Relapse			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Patient sex												
Female	1.00		-	-	1.00		-	-	1.00		-	-
Male	1.14 (0.79-1.64)	0.474	-	-	1.04 (0.69-1.56)	0.866	-	-	1.50 (0.65-3.48)	0.338	-	-
Sex matching												
Match	1.00		-	-	1.00		-	-	1.00		-	-
Mismatch	1.19 (0.83-1.70)	0.342	-	-	1.37 (0.92-2.04)	0.125	-	-	0.67 (0.29-1.56)	0.356	-	-
Age at transplantation												
49 years or younger	1.00		1.00		1.00		not selected		1.00		1.00	
50-59 years	1.08 (0.69-1.71)	0.728	1.08 (0.69-1.71)	0.730	0.82 (0.49-1.38)	0.455	not selected		3.80 (1.45-9.96)	0.007	3.08 (1.05-9.10)	0.041
Older than 59 years	2.50 (1.64-3.83)	<0.001	2.21 (1.42-3.44)	<0.001	1.73 (1.06-2.84)	0.029	not selected		4.92 (1.77-13.65)	0.002	2.96 (0.90-9.70)	0.073
Performance status at allo-HSCT												
0	1.00		-	-	1.00		-	-	1.00		-	-
1-4	1.34 (0.93-1.94)	0.120	-	-	1.28 (0.85-1.93)	0.240	-	-	1.67 (0.39-7.23)	0.492	-	-
Missing	0.85 (0.36-2.00)	0.710	-	-	0.72 (0.25-2.06)	0.541	-	-	0.74 (0.10-5.25)	0.762	-	-
Conditioning regimen												
MAC	1.00		not selected		1.00		-	-	1.00		1.00	
RIC	1.58 (1.10-2.27)	0.013	not selected		1.37 (0.92-2.04)	0.121	-	-	4.57 (1.78-11.76)	0.002	2.67 (0.98-7.28)	0.054
NMAC	0.98 (0.39-2.43)	0.964	not selected		0.21 (0.03-1.57)	0.129	-	-	10.81 (2.99-39.03)	<0.001	11.01 (2.55-47.54)	0.001
GVHD prophylaxis												
Cyclosporine-based	1.00		-	-	1.00		-	-	1.00		1.00	
Tacrolimus-based	1.18 (0.82-1.68)	0.377	-	-	1.26 (0.84-1.90)	0.257	-	-	1.26 (0.57-2.81)	0.567	2.06 (0.75-5.63)	0.159
Other	1.07 (0.26-4.38)	0.927	-	-	0.71 (0.10-5.17)	0.736	-	-	not calculated		not calculated	
Type of donor												
HLA-matched related donor	1.00		1.00		1.00		1.00		1.00		1.00	
HLA-mismatched related donor	1.78 (0.82-3.86)	0.143	1.78 (0.82-3.85)	0.146	2.53 (1.06-6.04)	0.037	2.44 (1.01-5.88)	0.047	not calculated		not calculated	
Unrelated bone marrow donor	1.12 (0.73-1.71)	0.598	1.07 (0.69-1.64)	0.771	1.71 (1.03-2.85)	0.039	1.64 (0.98-2.74)	0.060	0.35 (0.13-0.96)	0.042	0.28 (0.10-0.77)	0.014
Unrelated cord blood donor	2.22 (1.28-3.64)	0.004	1.77 (1.03-3.04)	0.037	2.58 (1.36-4.91)	0.004	2.55 (1.34-4.83)	0.004	1.88 (0.77-4.59)	0.168	1.12 (0.39-3.18)	0.836
Period of transplantation												
1999-2003	1.00		-	-	1.00		-	-	1.00		1.00	
2004-2008	0.78 (0.50-1.22)	0.280	-	-	1.01 (0.61-1.65)	0.981	-	-	0.30 (0.07-1.19)	0.087	0.19 (0.41-0.87)	0.033
2009-2012	0.81 (0.51-1.28)	0.369	-	-	0.77 (0.45-1.33)	0.350	-	-	1.51 (0.60-3.85)	0.384	0.90 (0.26-3.05)	0.863
Interval from diagnosis to allo-HSCT*												
17.5 months or shorter	1.00		-	-	1.00		-	-	1.00		-	-
Longer than 17.5 months	0.86 (0.60-1.24)	0.427	-	-	1.10 (0.73-1.64)	0.659	-	-	0.55 (0.24-1.24)	0.147	-	-
Use of ATG in the conditioning regimen												
No	1.00		-	-	1.00		-	-	1.00		-	-
Yes	1.28 (0.74-2.19)	0.373	-	-	1.44 (0.80-2.58)	0.224	-	-	0.36 (0.05-2.74)	0.327	-	-
Disease-altering therapy prior to allo-HSCT												
No treatment with disease-altering therapy	1.00		1.00		1.00		1.00		1.00		not selected	
ICT alone	2.15 (1.19 - 3.91)	0.012	2.10 (1.15-3.84)	0.016	2.21 (1.24 - 3.96)	0.007	2.05 (1.13-3.71)	0.018	1.94 (0.43 - 8.81)	0.391	not selected	
Azacitidine treatment alone	1.37 (0.34 - 5.57)	0.661	1.14 (0.28-4.65)	0.860	0.77 (0.12 - 5.04)	0.787	0.82 (0.11-5.88)	0.840	6.49 (1.52 - 27.66)	0.011	not selected	
ICT and azacitidine treatment	not calculated		not calculated	-	not calculated		not calculated	-	not calculated		not selected	

*The median interval from the diagnosis to allo-HSCT was 17.5 months in MDS with early disease status.

Supplemental Table 7. Causes of death among patients with early disease status

	No. of patients (%)					
	der(1;7)		-7/del(7q)		Normal	
Recurrence of MDS	3	(30.0)	2	(25.0)	21	(19.8)
Graft failure/rejection	0	(0.0)	0	(0.0)	5	(4.7)
GVHD	2	(20.0)	1	(12.5)	12	(11.3)
Infection	3	(30.0)	2	(25.0)	28	(26.4)
Idiopathic pneumonia	1	(10.0)	1	(12.5)	9	(8.5)
Organ failure	1	(10.0)	1	(12.5)	13	(12.3)
Secondary cancer	0	(0.0)	0	(0.0)	0	(0.0)
Bleeding	0	(0.0)	0	(0.0)	7	(6.6)
TMA	0	(0.0)	0	(0.0)	3	(0.0)
SOS	0	(0.0)	0	(0.0)	3	(2.8)
Other	0	(0.0)	1	(12.5)	5	(2.8)
Total	10	(100.0)	8	(100.0)	106	(100.0)

Supplemental Figure 1. Post-transplant outcomes by disease risk stratification



(A) The 3-year probabilities of overall survival (OS) after allo-HSCT were 69.8% (95% confidential interval [CI] 64.8-74.3%) and 49.3% (95% CI 44.8-53.3%) in patients with early and advanced disease status, respectively (P<.001). (B) The 3-year cumulative incidence rates of relapse (CIR) were 6.4% (95% CI 4.3-9.2%) and 22.6% (95% CI 19.3-26.1%) in patients with early and advanced disease status, respectively (P<.001). (C) The 3-year cumulative incidence rates of transplant-related mortality (TRM) were 24.1% (95% CI 19.8-28.6%) and 30.2% (95% CI 26.4-34.0%) in patients with early and advanced disease status, respectively (P=.071).