Multicenter Validation Study of a Transplantation-Specific Cytogenetics Grouping Scheme for Patients with Myelodysplastic Syndromes

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Abstract

Cytogenetics are an important prognostic factor for patients with MDS. However, existing cytogenetics grouping schemes are based on patients treated with supportive care, and may not be optimal for patients undergoing allogeneic stem cell transplantation (SCT). We previously proposed an SCT-specific cytogenetics grouping scheme for patients with MDS and AML arising from MDS, based on an analysis of patients transplanted at Dana-Farber Cancer Institute/Brigham and Women’s Hospital. Under this scheme, abnormalities of chromosome 7 and complex karyotype are considered adverse-risk, while all others are considered standard-risk. In the present retrospective study, we validated this scheme on an independent multicenter cohort of 546 patients. Adverse cytogenetics was the strongest prognostic factor for outcome in this cohort. Four-year relapse-free and overall survival were 42% and 46%, respectively, in the standard risk
group, versus 21% and 23% in the adverse group (*p*<0.0001 for both comparisons). This grouping scheme retained its prognostic significance irrespective of patient age, disease type, prior leukemogenic therapy, and conditioning intensity. Therapy-related disease was not associated with increased mortality in this cohort, after taking cytogenetics into account. We propose that this SCT-specific cytogenetics grouping scheme be used for patients with MDS or AML arising from MDS who are considering or undergoing SCT.

**INTRODUCTION**

Cytogenetics have for 20 years been recognized as an important prognostic factor for patients with myelodysplastic syndromes (MDS)\(^1\). The independent prognostic significance of cytogenetics has since been confirmed in several large patient series\(^2\)-\(^4\). Moreover, several series of patients undergoing allogeneic hematopoietic stem cell transplantation (SCT) have confirmed that cytogenetics retain their prognostic importance after SCT for patients with MDS or AML arising from MDS\(^5\)-\(^7\).

At present, the most commonly used cytogenetic risk grouping scheme is that of the International Prognostic Scoring System (IPSS)\(^2\) (which also forms part of the newer WHO Prognostic Scoring System (WPSS)\(^8\)), although refinements of this scheme have recently been proposed\(^3\),\(^4\),\(^9\). However, all of the patient cohorts on whom those schemes are based were treated primarily with supportive care (or only followed up to the time of aggressive therapy\(^9\)). Therefore, those schemes may not be optimal for patients who undergo SCT. Indeed, the success of SCT relies in part on an immunological graft-versus-tumor effect; sensitivity of the tumor cells to this effect may not correlate directly with their behavior in untreated disease or even with their sensitivity to conventional chemotherapy. A cytogenetics grouping scheme derived from a cohort of transplanted patients may then differ from the existing schemes, and may allow better prognostication and stratification of patients who undergo SCT. This is likely to be of growing importance as SCT is at present the only modality with curative potential in MDS, and, with the advent of reduced intensity conditioning, is being used for patients with MDS who are older or have a higher co-morbid burden.

We have previously proposed an SCT-specific cytogenetics grouping scheme, based on a retrospective study of Dana-Farber Cancer Institute/Brigham and Women’s Hospital (DFCI/BWH) patients\(^10\). In this scheme, patients with abnormalities of chromosome 7 or complex karyotype are considered “adverse-risk”, while all others are considered “standard-risk”. This scheme had a strong prognostic relevance in our cohort, regardless of disease type, stage, and conditioning regimen intensity. It had better stratification ability for patients with AML arising from MDS than any of the existing AML grouping schemes, arguing that cytogenetics risk assignment for those patients should be based on an MDS-specific scheme rather than an AML-specific scheme. This is relevant since the WHO classification\(^11\) categorizes those patients as AML (including patients formerly categorized as having refractory anemia with excess blasts in transformation (RAEB-t)), without addressing the question of how best to characterize their cytogenetics for prognostic purposes. Moreover, we showed that patients with therapy-related disease had a prognosis after SCT similar to
that of patients with *de novo* disease, after adjusting for cytogenetics risk, as was also reported by the Seattle group. In the present study, we report the multicenter validation of these findings in an independent large cohort of patients from three separate transplantation centers.

**MATERIALS AND METHODS**

**Patients**

We analyzed data on 546 adult patients with MDS who underwent allogeneic SCT at the Fred Hutchinson Cancer Research Center (FHCRC) or the M.D. Anderson Cancer Center (MDACC) between 1996 and 2007, or at Princess Margaret Hospital (PMH) between 2001 and 2007. We included patients with acute myelogenous leukemia (AML) who had a prior diagnosis of MDS (considered as “AML with MDS-related changes” under the 2008 WHO classification), and patients with 20-30% marrow blasts (formerly characterized as RAEB-t); those 2 groups are collectively referred to herein as “AML/MDS”. We excluded patients who had received a prior stem cell transplant, whether autologous or allogeneic, unless they had received an autologous transplant for a disease other than MDS or AML (i.e., for patients with therapy-related MDS/AML). Ninety-three patients, who had received alkylating agent chemotherapy, a topoisomerase II inhibitor, or radiotherapy, at least one year before the diagnosis of MDS, were categorized as having “therapy-related disease”, as opposed to the remaining 453 patients with “*de novo* disease”. Cytogenetics were obtained from the medical records. For patients with evidence of cytogenetic evolution, the latest karyotype before SCT was used for the analysis.

IRB approval was obtained from all the participating institutions to perform this study, in accordance with the principles of the Declaration of Helsinki.

**Treatment**

Transplantation protocols, as expected, varied by transplantation center. Two thirds of patients received a conventional intensity conditioning regimen, which included total body irradiation (TBI) in 30% of patients. A lower proportion of MDACC received a conventional intensity regimen (21%, compared to 77% for FHCRC and 68% for PMH, \( p<0.0001 \)); conventional intensity regimens at MDACC were all based on fludarabine + melphalan, whereas patients at FHCRC and PMH received mostly cyclophosphamide + TBI or cyclophosphamide + busulfan for conventional intensity SCT. Among the patients who received a reduced intensity regimen, 42% received low-dose TBI as part of their conditioning. Sixty-five percent of patients received peripheral blood progenitor cells as a source of stem cells. The donors were HLA-identical siblings for 46% of patients, matched unrelated donors for 36%, and HLA-mismatched donors (related or unrelated) in the remaining 18%. Graft-versus-host disease (GVHD) prophylaxis consisted mostly of a calcineurin inhibitor (cyclosporine or tacrolimus) combined with methotrexate (73%), or cyclosporine with mycophenolate mofetil (MMF) (12%).
Statistics

Patient baseline characteristics were treated descriptively. Overall survival and relapse-free survival were calculated using the Kaplan-Meier method. Overall survival was defined as the time from stem cell infusion to death from any cause. Patients who were alive or lost to follow-up were censored at the time last seen alive. Relapse-free survival was defined as the time from stem cell infusion to relapse or death from any cause. Patients who were alive without relapse were censored at the time last seen alive and relapse-free. The log-rank test was used for comparisons of Kaplan-Meier curves. Cumulative incidence curves for non-relapse death and relapse with or without death were constructed reflecting time to relapse and time to non-relapse death as competing risks. The difference between cumulative incidence curves in the presence of a competing risk was tested using the Gray method. Time to relapse and time to non-relapse death were measured from the date of stem cell infusion. Potential prognostic factors for survival, relapse-free survival, relapse, and non-relapse death were examined in the proportional hazards model as well as in the competing risks regression model. All interaction terms including interaction with time were examined in the proportional hazards regression model. Proportional hazards assumptions for all important variables were examined. For our analysis of AML/MDS patients, we compared model fit using various classification options by comparing the Akaike Information Criterion (AIC) between models. All calculations were done using SAS 9.2 (SAS Institute Inc, Cary, NC) and R (version 2.5.1).

RESULTS

Patient characteristics and cytogenetics

The baseline demographic and clinical characteristics of the 546 patients enrolled in this study are presented in Table 1. The median age for the entire cohort was 53 (range, 18-74) years. Patients transplanted at MDACC were on average older (median age 59 versus 52 for FHCRC and 53 for PMH, p<0.0001). Fifty-seven percent of the patients had MDS (as defined by the WHO criteria); among those, 30% had low-risk MDS (including refractory anemia with or without ringed sideroblasts, refractory cytopenias with multilineage dysplasia with or without ringed sideroblasts, and 27% had high-risk MDS (refractory anemia with excess blasts (RAEB-1 or RAEB-2)). The 8 patients with chronic myelomonocytic leukemia were classified as low-risk, based on a comparison of their outcome with the low-risk and high-risk groups. Thirty-nine percent of patients had AML and a prior diagnosis of MDS, and 4% had AML but would previously have been classified as having RAEB-t. Seventeen percent of patients were considered to have therapy-related disease. Most of the patients (61%) were transplanted without having received pre-SCT therapy; 13% were transplanted in complete remission; the remaining 26% were transplanted with active disease (10% in partial remission, 5% after induction failure, and 10% with active relapsed disease). Patients from MDACC more frequently had advanced stage disease at SCT (68% versus 8% for FHCRC and 9% for PMH, p<0.0001). The median time from diagnosis to transplantation was 7 (range, 0-634) months. Patients from MDACC tended to be transplanted farther from diagnosis (after a median of 13 months, compared to 7 for FHCRC and 5 for PMH, p<0.0001). The follow-up for survivors was 6-135 (median 48) months.
Table 2 details pre-transplantation cytogenetic findings for all patients. Data were available in 86% of patients; for the remaining 14%, cytogenetics had either not been obtained or the results were not available. Among all patients, when grouped according to the IPSS/WPSS scheme, 40% had favorable, 21% had intermediate, and 24% had adverse cytogenetics. There was no significant difference between the 3 centers in the proportions of patients in each cytogenetics group. The most common finding was a normal karyotype (32% of patients). The patients with unavailable cytogenetics had significantly worse overall survival (OS), with 4-year OS of 27% versus 40% for patients with available cytogenetic data ($p=0.007$). However, patients without cytogenetic information tended to be transplanted in the earlier years of the study ($p=0.02$), which could have confounded the results. Indeed, in a proportional hazards model including both availability of cytogenetics and year of transplantation, availability of cytogenetics data lost its prognostic significance (hazard ratio (HR)=0.97, $p=$ not significant). Those patients were not further considered in the subsequent analyses.

As expected, patients with therapy-related disease more often had poor-risk cytogenetics. Only 30% of patients with therapy-related disease had favorable cytogenetics, compared to 51% of patients with de novo disease ($p=0.0007$); 21% of patients with therapy-related disease had intermediate cytogenetics, compared to 26% of patients with de novo disease ($p=0.5$); and 49% of patients with therapy-related disease had poor-risk cytogenetics, compared to 24% of patients with de novo disease ($p<0.0001$) (see Table 2).

Patients with adverse cytogenetics tended to be transplanted earlier in the course of their disease (median time from diagnosis to SCT 6 months compared to 8 months for patients with intermediate or favorable cytogenetics, $p<0.0001$). This was true even after stratifying for stage of disease at SCT (not shown).

**Derivation of the cytogenetics risk groups**

The 4-year overall survival (OS) and relapse-free survival (RFS) for the entire cohort were 40% (95% confidence interval (CI), 35-44%), and 36% (CI, 31-40%), respectively. Cytogenetics (classified according to the IPSS/WPSS scheme), along with transplantation center and all the baseline variables from Table 1 (except for prior autologous transplantation for patients with therapy-related disease, given the small sample size), were entered into a proportional hazards model for OS. Since graft source and GVHD prophylaxis regimens violated proportional hazards assumptions, but were not significantly associated with outcome (not shown), the models were stratified on those two variables. Among the remaining variables, cytogenetics, disease type and stage, and year of transplantation were significant for outcome. Based on the results of the models, disease was dichotomized into “early stage” (untreated patients and patients in complete remission) and “advanced stage” (patients with induction failure, partial remission or active relapse at the time of transplantation). Age was dichotomized with a cut-off of 50 years, although it was not a significant prognostic factor regardless of the cut-off chosen. For RFS, the same variables were significant, except for year of transplantation, which showed only a trend towards significance. Those variables were then included in a multivariable model with each cytogenetic abnormality entered as a separate term. The results are given in Table 3. Two
distinct prognostic groups can be clearly separated: an “adverse-risk” group comprising any abnormality of chromosome 7 and complex karyotypes (≥3 abnormalities); and a “standard-risk” group comprising all other abnormalities, including normal karyotype, del(5q), and del(20q) (which are considered favorable in the IPSS/WPSS scheme). This grouping system is identical to the one that we proposed earlier based on our DFCI/BWH data.

We also analyzed the impact of monosomy-containing karyotypes, since those have been associated with adverse prognosis in AML. In our cohort, there were 47 instances of non-complex karyotypes containing a monosomy abnormality. Of those, 9 did not involve chromosome 7, and of those only 3 had isolated monosomy karyotypes (including 2 with monosomy Y). A non-7 monosomy-containing karyotype appeared to be associated with worse OS after transplantation (HR=2.6, \(p=0.013\)); however, there was no significant adverse prognosis for isolated non-7 monosomy karyotypes. The small number of patients involved, however, precluded reliable conclusions.

Survival, relapse and non-relapse mortality

The 4-year OS for patients in the standard-risk cytogenetics group was 46% (CI, 40-52%), compared to 23% (CI, 16-30%) in the adverse-risk group (\(p<0.0001\)). The corresponding figures for RFS were 42% (CI, 36-47%) versus 21% (CI, 14-28%) (\(p<0.0001\)). The 4-year cumulative incidence of relapse in the standard-risk cytogenetics group was 22% (CI, 17-27%) compared to 41% in the adverse-risk group (CI, 33-50%) (\(p<0.0001\)), while the cumulative incidence of NRM was 36% (CI, 31-42%) versus 38% (CI, 29-46%) (\(p=0.4\)).

The corresponding curves are shown in Figure 1.

We repeated the multivariable analyses for OS and RFS using the new cytogenetics grouping scheme. We also built regression models for relapse and non-relapse mortality (NRM). The results are shown in Table 4. Adverse cytogenetics, as defined in the previous section, was associated with a HR for mortality of 2.2 (\(p<0.0001\)), and a similar HR for death or relapse, compared to standard-risk cytogenetics. This difference was due to an increased risk of relapse (HR for relapse 2.0, \(p=0.0004\)), without a significant effect on NRM (HR=1.4, \(p=0.07\)). As before, disease type and stage as well as year of transplantation were significant factors for OS.

We then examined the prognostic significance of our cytogenetics grouping scheme in various patient subgroups. The results (not shown) show that cytogenetics retained their prognostic relevance regardless of patient age (<50 or ≥50), disease type (MDS or AML/MDS), conditioning regimen intensity (conventional or reduced intensity), or receipt of prior leukemogenic therapy. Within each subgroup, patients with adverse cytogenetics had significantly worse OS (all \(p<0.01\)). In fact, there was no significant interaction between cytogenetics risk group and any of the other variables in the proportional hazards model.

In order to summarize the outcomes of various patient subgroups stratified by cytogenetics, we merged the present cohort with the original DFCI/BWH cohort of 227 patients in which the scheme was originally derived. The OS and RFS within each subgroup are shown in Table 5.
Classification of cytogenetics for patients with AML/MDS

Since it is not known whether patients with AML/MDS (including patients with AML and a prior diagnosis of MDS and patients formerly characterized as having RAEB-t) should be classified as MDS patients or as AML patients with respect to cytogenetics, we sought to determine the optimal grouping scheme for this patient group in our cohort. We built proportional hazards model for OS for only those 233 patients, and compared the model fit (based on Akaike’s Information Criterion (AIC), with a lower score indicating a better model fit). The AIC for our proposed scheme (AIC=2089) was lower than the AIC using the MRC grouping scheme for AML (AIC=2090), the CALGB scheme (AIC=2106), the SWOG/ECOG scheme (AIC=2097), or our previously proposed AML grouping scheme (AIC=2093). This argues that cytogenetics for those patients are better characterized according to our MDS-specific scheme than according to an AML-specific one. Using our proposed scheme, the HR associated with adverse cytogenetics for this patient subgroup was 2.2 ($p<0.0001$).

DISCUSSION

In a previous study of data from 227 patients transplanted at DFCI/BWH, we proposed a cytogenetics grouping scheme specifically applicable to patients with MDS or AML arising from MDS undergoing SCT. In the present study, we performed a similar analysis on an entirely independent, multicenter cohort of 546 patients. We showed not only that our previously proposed scheme allowed prognostic stratification in this new cohort, but that a new grouping scheme derived from scratch led to the identical scheme, which lends strong support to the broad applicability of the originally proposed scheme. In the current study, we were also able to further refine the scheme by classifying patients with del(5q) or del(20q) in the standard-risk category (which we could not classify in our original study given the limited sample size of those patients). The present results confirm that patients with MDS or AML arising from MDS undergoing SCT may be categorized into two distinct risk groups based on their karyotype; patients with abnormalities of chromosome 7 and patients with complex cytogenetics ($\geq 3$ abnormalities) have an adverse prognosis compared to all other abnormalities, which have a similar prognosis to patients with normal karyotype. We still had too few patients with monosomy Y to allow reliable classification of this subgroup, although the limited data available suggested that they were best considered standard risk as well.

Our proposed scheme is similar to the IPSS2/WPSS8 scheme. However, the favorable and intermediate categories are now grouped together into a “standard-risk” category. Indeed, when the patients in our cohort are grouped according to the IPSS/WPSS scheme, the OS of patients in the favorable and intermediate categories are indistinguishable (Figure 2). The absence of a favorable group is consistent with other transplantation series (although those studies were not designed to establish an optimal grouping scheme, and one of them overlaps with our validation cohort). In the study of Alessandrino et al., cytogenetics had a significant effect on the risk of relapse (and no significant effect on NRM), without a significant difference between the favorable and intermediate IPSS groups. The same was basically true in the study of Chang et al., although over long follow-up the intermediate
risk cytogenetic group showed more of an intermediate position in its risk of relapse. There is no obvious explanation for this discrepancy; but the study of Chang et al. included the largest sample of patients with therapy-related disease, and may, therefore, have had more power to detect a difference in the relapse rate specific to this population. Even so, in all of those studies, the RFS and OS were not significantly different between the IPSS favorable and intermediate groups, in agreement with the major conclusion of the present study.

Several limitations of the present analysis deserve comment. First, just like our prior report, this was a retrospective study which always carries the potential of selection bias. For example, clinicians may transplant patients with adverse cytogenetics earlier than others (as we observed here), which may narrow the observed difference in outcomes. Second, because of the retrospective nature of this analysis, we did not require central review of primary cytogenetics data, which would be practically and logistically impossible in a multicenter study of this size. However, the large sample size of this study should limit the impact of random errors in the cytogenetics assignment. Third, this study did not make systematic use of FISH to detect karyotypically silent abnormalities, in particular del(5q), monosomy 7 or trisomy 8. The rate of karyotypically silent abnormalities detected by FISH varies by series, although it was low in a large study of AML patients. If patients with FISH-detected abnormalities have a similar outcome to those with karyotypically overt ones, this could also narrow the apparent survival gap between the groups, or worsen the apparent outcome of patients with apparently normal cytogenetics. Fourth, newer prognostic markers, such as molecular abnormalities or flow cytometry abnormalities, may modulate the importance of cytogenetics, but were not available for this study. Finally, we only used the disease karyotype closest to the time of SCT for analysis. It would be interesting to study the prevalence and impact of karyotypic evolution. However, because of the retrospective nature of this study, we could not systematically analyze karyotypic evolution for patients. Nevertheless, it seems reasonable to assume that the karyotype closest to the time of transplantation will be the one most important for transplantation outcome, and we therefore chose this karyotype for our analyses.

Despite those limitations, the proposed cytogenetics grouping scheme has high prognostic significance for patients with MDS or AML arising from MDS who undergo SCT. It proved very successful at stratifying an independent cohort of patients. Indeed, in the present study, patients in the two cytogenetics groups showed highly significant differences in overall and relapse-free survival after transplantation. In both the original study and the current analysis, adverse cytogenetics was the strongest prognostic factor for OS and RFS. Moreover, as in our prior study, we found that this difference was entirely dependent on an increased risk of relapse in the adverse group. This was to be expected from the fact that cytogenetics are more a function of the disease itself than the host’s ability to withstand transplantation. Importantly, we could also confirm that cytogenetics remain highly prognostically significant regardless of patient age, disease type or stage, and conditioning regimen intensity. The prognostic importance of cytogenetics after reduced intensity conditioning SCT argues that tumors with adverse cytogenetics are more resistant to the graft-versus-leukemia effect than tumors with standard risk cytogenetics, just as they are more resistant to conventional therapy.
As previously reported by Armand et al.10 and Chang et al.7, the present study shows that therapy-related disease per se is not an adverse prognostic factor after SCT, after accounting for cytogenetics risk group (which otherwise may confound comparisons, since patients with therapy-related disease more often have adverse cytogenetics25-29). This finding, now confirmed from several institutions, is important since patients with therapy-related disease have a poor outcome with conventional therapy27,30. The fact that this does not seem to be true for patients undergoing SCT supports (at least indirectly) the practice of offering SCT to patients with therapy-related disease early in their treatment course.

The validated transplantation-specific cytogenetics grouping scheme presented here could be used in the selection and counseling of SCT candidates. The fact that cytogenetics was the strongest prognostic factor in both our original study and the present ones argues for considering stratification of patients in clinical trials by cytogenetics, and our proposed scheme provides a means for doing so. Finally, this scheme may be used to calibrate transplantation outcomes among centers, under the new federal reporting rules.

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Figure 1. Survival, relapse and non-relapse mortality, by cytogenetics group (proposed scheme)
(A) Overall Survival; (B) Relapse-free survival. (C) Cumulative incidence of relapse. (D) Cumulative incidence of non-relapse mortality.
Figure 2. Overall survival, by cytogenetics group (IPSS/WPSS scheme)
Table 1

Baseline characteristics of the patients

| Variable | N. (%) |
|----------|--------|
| **Number of patients** | 546 |
| Age (years) (median, range) | 53 (18-74) |
| **Disease** | |
| Low-risk MDS (RA/RARS/RCMD/RCMD-RS/CMML) | 164 (30) |
| High-risk MDS (RAEB-1/2) | 149 (27) |
| AML/MDS | 233 (43) |
| RAEB-t | 21 (4) |
| AML with prior diagnosis of MDS | 212 (39) |
| **Therapy-related disease** | |
| ASCT for primary disease | 93 (17) |
| **Stage at SCT** | |
| Untreated | 332 (61) |
| CR | 70 (12) |
| Induction failure/PR | 87 (16) |
| Relapse | 57 (10) |
| **Donor match** | |
| MRD | 251 (46) |
| MUD | 195 (36) |
| Mismatched | 100 (18) |
| MMRD | 23 (4) |
| MMUD | 77 (14) |
| **Graft source** | |
| PB | 354 (65) |
| BM | 187 (34) |
| Cord blood | 5 (1) |
| **Conditioning** | |
| Conventional | 374 (68) |
| Reduced intensity | 172 (32) |
| **GVHD prophylaxis** | |
| CsA/steroids | 15 (3) |
| CsA/Mtx | 401 (73) |
| CSA/MMF | 67 (12) |
| Not available | 63 (12) |
| **CMV serostatus** | |
| Recipient or donor + | 364 (67) |
| **Gender mismatch** | 236 (43) |
| **Year of SCT (median, range)** | 2002 (1996-2007) |
| **Time from diagnosis to SCT (months)(median, range)** | 7 (0-634) |
| **Center** | |
| PMH | 47 |
| MDACC | 72 |
| FHCRC | 427 |
| **Months of follow-up** (median, range) | 48 (6-135) |

Percentages may not add to 100 because of rounding.

MDS indicates myelodysplastic syndromes; RA, refractory anemia; RARS, refractory anemia with ringed sideroblasts, RCMD, refractory cytopenias with multilineage dysplasia; RCMD-RS, refractory cytopenias with multilineage dysplasia with ringed sideroblasts; CMML, chronic myelomonocytic leukemia; RAEB, refractory anemia with excess blasts; RAEB-t, RAEB in transformation; AML, acute myelogenous leukemia; ASCT, autologous stem cell transplantation; SCT, allogeneic stem cell transplantation; CR, complete remission; PR, partial remission; MRD, matched related donor; MUD, matched unrelated donor; MMRD, mismatched related donor; MMUD, mismatched unrelated donor; PB, peripheral bone marrow.
blood; BM, bone marrow; GVHD, graft-versus-host disease; CnI, calcineurin inhibitor (cyclosporine or tacrolimus); Mtx, methotrexate; MMF, mycophenolate mofetil; and CMV, cytomegalovirus.

\(^a\)CMML was included in the low-risk category based on its similar outcome to other low-risk patients in this cohort

\(^b\)For survivors.
Table 2
Cytogenetics by IPSS/WPSS classification

| Cytogenetics       | De novo disease N. (%) | Therapy-related N. (%) | P    | Total N. ( % )a |
|--------------------|------------------------|------------------------|------|-----------------|
| Number of patients |                        |                        |      | 546             |
| Not available      | 68 (15)                | 9 (10)                 | 0.2  | 77 (14)         |
| Favorable          |                        |                        |      | 220 (40)        |
| Del(5q)            | 195 (43)               | 25 (27)                | 0.004| 220 (40)        |
| Del(20q)           | 20 (4)                 | 1 (1)                  |      | 21 (4)          |
| Monosomy Y         | 2 (0)                  | 0 (0)                  |      | 2 (0)           |
| Normal             | 152 (34)               | 24 (26)                |      | 176 (32)        |
| Intermediate       |                        |                        |      | 117 (21)        |
| Trisomy 8          | 99 (22)                | 18 (19)                | 0.7  | 117 (21)        |
| All others         | 57 (13)                | 16 (17)                |      | 73 (13)         |
| Adverse            |                        |                        |      | 132 (24)        |
| Abnormal 7         | 91 (20)                | 41 (44)                | <0.0001| 132 (24)     |
| Complex (≥3)       | 62 (14)                | 22 (24)                |      | 84 (15)         |

Percentages may not add to 100 because of rounding.
Abbreviations are as in Table 1.

\(^a\) Includes 5 patients with both 5 and 7 abnormalities.
### Table 3
Multivariable OS model for cytogenetics risk group determination

| Variable                      | HR    | p       | Risk group |
|-------------------------------|-------|---------|------------|
| **Disease**                   |       |         |            |
| Low-risk MDS (RA/RARS/RCMD/RCMD-RS/CMML) | 1.6   | 0.005   |            |
| High-risk MDS (RAEB-1/2)      | 1.6   | 0.005   |            |
| AML/MDS<sup>a</sup>           |       |         |            |
| **Stage at SCT<sup>b</sup>**  |       |         |            |
| Early                        | 1.4   | 0.018   |            |
| Advanced                     |       |         |            |
| **Year of transplantation**   |       |         |            |
| Before 2002                  | 0.7   | 0.007   |            |
| 2002 or after                |       |         |            |
| **Cytogenetic abnormality**   |       |         |            |
| Normal karyotype             | 1.3   | 0.4     | Standard   |
| Del(5q)                      | 0.9   | 0.9     |            |
| Del(20q) or monosomy Y<sup>c</sup> | 0.8   | 0.3     |            |
| Trisomy 8                    | 1.1   | 0.5     |            |
| All others                   |       |         |            |
| Abnormal 7                   | 1.8   | 0.004   | Adverse    |
| Complex                      | 2.4   | <0.0001 |            |

HR indicates hazard ratio; Ref, reference group; other abbreviations are as in Table 1.

<sup>a</sup> Including patients with 20-30% marrow blasts and patients with AML and a prior diagnosis of MDS

<sup>b</sup> Early stage includes untreated patients and patients in complete remission; advanced stage includes patients with induction failure, partial remission or active relapse at the time of transplantation.

<sup>c</sup> Since there were only 2 patients with monosomy Y, they were grouped with the del(20q) patients.
Table 4

Multivariate analyses using new cytogenetics risk groups

| Variable                        | OS   | RFS  | Relapse | NRM  |
|---------------------------------|------|------|---------|------|
|                                 | HR   | p    | HR      | p    |
| **Cytogenetics**                |      |      |         |      |
| Standard risk                   | 1.0  | Ref  | 1.0     | Ref  |
| Adverse                         | 2.2  | <0.0001 | 2.2   | <0.0001 |
| **Age ≥ 50**                    | 1.2  | 0.3  | 1.3     | 0.082 |
| **Disease**                     |      |      |         |      |
| Low-risk MDS\(a\)               | 1.0  | Ref  | 1.0     | Ref  |
| High-risk MDS\(a\)              | 1.5  | 0.014 | 1.5    | 0.014 |
| AML/MDS\(a\)                    | 1.3  | 0.069 | 1.4    | 0.028 |
| **Therapy-related disease**     | 0.9  | 0.6  | 1.0     | 0.9  |
| **Stage at SCT**\(b\)           |      |      |         |      |
| Early                           | 1.0  | Ref  | 1.0     | Ref  |
| Advanced                        | 1.5  | 0.010 | 1.4   | 0.022 |
| **Donor match**                 |      |      |         |      |
| Matched                         | 1.0  | Ref  | 1.0     | Ref  |
| Mismatched                      | 1.2  | 0.2  | 1.3     | 0.12 |
| **Graft source**                |      |      |         |      |
| PB\(c\)                         | NA\(d\) | NA\(d\) | 1.0   | 0.9  |
| BM                              |      |      |         |      |
| **Conditioning**                |      |      |         |      |
| Conventional                    | 1.0  | Ref  | 1.0     | Ref  |
| Reduced intensity               | 1.2  | 0.3  | 1.1     | 0.4  |
| **GVHD prophylaxis**            |      |      |         |      |
| CNP/MoX                         | NA\(d\) | NA\(d\) | 1.0   | 1.2  |
| Other                           |      |      |         |      |
| **CMV serostatus**              |      |      |         |      |
| Recipient or donor +            | 1.1  | 0.5  | 1.1     | 0.7  |
| **Gender mismatch**             |      |      |         |      |
|                                 | 1.1  | 0.6  | 1.1     | 0.4  |
| **Year of SCT**                 |      |      |         |      |
| Before 2002                     | 1.0  | Ref  | 1.0     | Ref  |
| 2002 or later                   | 0.8  | 0.045 | 0.8    | 0.11 |
| **Months from dx to SCT**       |      |      |         |      |
|                                 | 1.0  | 0.2  | 1.0     | 0.3  |
| **Center**                      |      |      |         |      |
| FHCRC                           | 1.0  | Ref  | 1.0     | Ref  |
| MDACC                           | 1.0  | 0.9  | 0.9     | 0.6  |
| PMH                             | 1.0  | 0.6  | 1.0     | 0.9  |
See table 1 for definitions.

Early stage includes untreated patients and patients in complete remission; advanced stage includes patients with induction failure, partial remission or active relapse at the time of transplantation.

Includes 3 patients who received an umbilical cord blood transplantation.

As discussed in the text, those variables were not entered into the model since they did not satisfy the proportional hazards assumptions; instead, the models were stratified on them.
| Subgroup             | 4-year OS (%, CI) | 4-year RFS (%, CI) |
|---------------------|------------------|-------------------|
|                     | %, a             | p, b              | %, a             | p, b              |
| **All patients**    |                  |                   |                  |                   |
| Standard            | 44 (40-49)       | <0.0001           | 40 (35-45)       | <0.0001           |
| Adverse             | 20 (15-26)       |                   | 17 (12-23)       |                   |
| **Age**             |                  |                   |                  |                   |
| <50                 | 78 (48-56)       | <0.0001           | 45 (38-53)       | <0.0001           |
| ≥50                 | 22 (36-48)       |                   | 17 (31-43)       |                   |
| **Disease**         |                  |                   |                  |                   |
| MDS                 | 52 (45-58)       | <0.0001           | 47 (40-53)       | <0.0001           |
| AML/MDS             | 35 (28-42)       |                   | 32 (25-38)       |                   |
| **Conditioning**    |                  |                   |                  |                   |
| Conventional        | 48 (42-53)       | <0.0001           | 44 (38-49)       | <0.0001           |
| RIC                 | 38 (29-47)       |                   | 33 (25-41)       |                   |
| **Disease**         |                  |                   |                  |                   |
| De novo             | 44 (39-50)       | <0.0001           | 40 (35-45)       | <0.0001           |
| Therapy-related     | 45 (31-59)       | <0.0001           | 39 (25-53)       | <0.0001           |

Those results are based on the group of 773 patients obtained from merging the training cohort from DFCI/BWH and the present validation cohort from MDACC, PMH and FHCRC.

RIC indicates reduced intensity conditioning; other abbreviations are as in Tables 1, 3, and 4.

*Percentage of patients in each subgroup*