

Impact of the revised International Prognostic Scoring System, cytogenetics and monosomal karyotype on outcome after allogeneic stem cell transplantation for myelodysplastic syndromes and secondary acute myeloid leukemia evolving from myelodysplastic syndromes: a retrospective multicenter study of the European Society of Blood and Marrow Transplantation

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ABSTRACT

The aim of this study was to determine the impact of the revised 5-group International Prognostic Scoring System cytogenetic classification on outcome after allogeneic stem cell transplantation in patients with myelodysplastic syndromes or secondary acute myeloid leukemia who were reported to the European Society for Blood and Marrow Transplantation database. A total of 903 patients had sufficient cytogenetic information available at stem cell transplantation to be classified according to the 5-group classification. Poor and very poor risk according to this classification was an independent predictor of shorter relapse-free survival (hazard ratio 1.40 and 2.14), overall survival (hazard ratio 1.38 and 2.14), and significantly higher cumulative incidence of relapse (hazard ratio 1.64 and 2.76), compared to patients with very good, good or intermediate risk. When comparing the predictive performance of a series of Cox models both for relapse-free survival and for overall survival, a model with simplified 5-group cytogenetics (merging very good, good and intermediate cytogenetics) performed best. Furthermore, monosomal karyotype is an additional negative predictor for outcome within patients of the poor, but not the very poor risk group of the 5-group classification. The revised International Prognostic Scoring System cytogenetic classification allows patients with myelodysplastic syndromes to be separated into three groups with clearly different outcomes after stem cell transplantation. Poor and very poor risk cytogenetics were strong predictors of poor patient outcome. The new cytogenetic classification added value to prediction of patient outcome compared to prediction models using only traditional risk factors or the 3-group International Prognostic Scoring System cytogenetic classification.

Introduction

Currently, the most effective curative treatment approach for patients with myelodysplastic syndromes (MDS) or secondary acute myeloid leukemia (sAML) evolving from MDS is allogeneic stem cell transplantation (SCT).¹ With the introduction of reduced intensity conditioning (RIC), the non-relapse mortality (NRM) could be lowered, especially in older patients.^{2,3} However, disease relapse is the most important factor for long-term overall survival (OS) after SCT in patients surviving the (acute) treatment-related toxicity.⁴ Besides stage of the disease (e.g. number of marrow blasts, time from diag-

nosis to transplant, prior chemotherapeutic treatment and remission status), the karyotype of the disease seems to be most predictive for relapse-free survival (RFS) after transplantation.⁵⁻¹⁵ However, most studies used the International Prognostic Scoring System (IPSS) cytogenetic risk score (good, intermediate, and poor cytogenetic risk groups) for the analysis of relapse and OS after SCT in MDS patients.¹⁶ In 2012, a new 5-group cytogenetic scoring system with a refined cytogenetic risk prediction in MDS patients not undergoing SCT was proposed.¹⁷ This scoring system includes clonal abnormalities, which have been underrepresented in the IPSS cytogenetic risk score categories. Therefore, the 5-group cyto-

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netic risk classification entered the revised IPSS (IPSS-R) scoring system for patients with MDS, which was renewed in 2012 accordingly.¹⁸

The impact of the revised IPSS-R for MDS patients undergoing SCT was analyzed in one single center study,¹³ and more recently in a national multicenter study.¹⁴ These studies have shown that the novel classification has greater discriminating power for OS and relapse after SCT than the old IPSS classification. In contrast to the latter studies, we focused only on cytogenetic information of the novel 5-group IPSS-R classification to evaluate the outcome of MDS and sAML patients after SCT in an analysis based on a large cohort from the European Society for Blood and Marrow Transplantation (EBMT) database. The analysis was performed using the latest available karyotype before transplantation, restricted to measurements within one year before SCT.

In addition to previous findings^{13,14} which also focus on IPSS-R cytogenetics and SCT, we show that poor and very poor risk cytogenetics, within the IPSS-R-cytogenetic risk categories, are strong predictors of poor outcome after transplantation, also when other risk factors are considered simultaneously. Furthermore, the presence of a monosomal karyotype (MK) has an additional impact on RFS and OS, but only in the poor risk group and not in the very poor risk cytogenetics group of patients.

Methods

Patients with MDS or sAML with available cytogenetic information within 12 months before transplantation and an HLA-matched donor were identified from the EBMT-database. Cytogenetic information, as reported to the database, was reviewed and classified according to MK, IPSS¹⁶ and IPSS-R.¹⁸ Patients who received more than one allograft were kept in the analysis and the outcome of the first SCT was used. Base-line information, transplant-characteristics and follow-up information of patients were down-loaded from the database.

Definition of disease status at SCT

Disease status at SCT was defined according to the FAB¹⁹ or WHO classification,²⁰ to remission status and to prior chemotherapy. These definitions led to 4 patient groups: 1) patients with refractory anemia (RA), RA with ringsideroblasts (RARS) or refractory cytopenias with multilineage dysplasia (RCMD) who had never had higher MDS-stages (RA with excess of blasts, RAEB; chronic myelomonocytic leukemia, CMML, sAML) and who did not receive chemotherapy before SCT; 2) RAEB or RAEB in transformation (RAEB(t))/sAML/CMML without induction chemotherapy and, therefore, not in remission; 3) RAEB or RAEB(t)/sAML/CMML with induction chemotherapy leading to complete remission (CR); 4) RAEB or RAEB(t)/sAML/CMML with refractory disease or relapse after induction chemotherapy.

We did not include percentage of bone marrow blasts in our analysis since our definition of patient groups contains this information. Patients who received hypomethylating agents were considered as patients without chemotherapy, since statistical comparison showed that there was no difference between outcomes of RAEB(t)/sAML/CMML patients in CR respectively not in CR after treatment with hypomethylating agents and outcomes of patients in CR respectively not in CR who did not receive hypomethylating agents (*data not shown*). Less than 5% of all patients had CMML.

Table 1. Patients' and disease characteristics of MDS/sAML patients (n=903).

	N. (%)
Patient age (years)	
Median (range)	50.0 (18-74)
Patient sex*	
Male	500 (55.4)
Female	402 (44.6)
Disease status at transplant**	
RA/RARS/RCMD without treatment	97 (10.7)
RAEB/sAML/CMML in CR	218 (24.1)
RAEB/sAML/CMML not in CR	250 (27.7)
RAEB/sAML/CMML untreated	227 (25.1)
Cytogenetic risk (IPSS, 3-group)	
Good	192 (21.3)
Intermediate	500 (55.4)
Poor	211 (23.4)
Cytogenetic risk (IPSS-R, 5-group)	
Very good	19 (2.1)
Good	204 (22.6)
Intermediate	438 (48.5)
Poor	178 (19.7)
Very poor	64 (7.1)

*Missing in one patient. **Unknown in 111 patients.

Statistical analysis

The primary end point for this analysis was RFS, defined as the time from transplantation to death or disease progression, with surviving patients censored at the last time point reported alive and disease-free.²¹ OS was defined as the time from SCT to death, with surviving patients censored at the last time point reported alive. Cumulative incidence of relapse (CIR) was defined as time from transplantation to disease progression. Non-relapse mortality (NRM) was defined as time from transplantation to death before disease progression. RFS and OS were analyzed in stratified Kaplan-Meier curves, comparing outcomes for different groups by means of two-sided log ranks tests. Similarly, CIR and NRM were analyzed by means of cumulative incidence curves, testing for differences by means of the Gray test.²²

The impact of cytogenetic classifications in combination with other risk factors was assessed in multivariate Cox regression models for RFS and OS. Results of these analyses were used to create simplified versions of the classifications. Model fit of multivariate models for each outcome was compared by means of the Akaike information criterion (AIC). Predictive performance of models was compared by means of the cross-validated log partial likelihood.²³

Explorative analyses of competing risks outcomes were made in multivariate Cox models for cause-specific hazards, including as predictors those selected in the OS and RFS models.

Software used was SPSS 20 (IBM SPSS Statistics) and R 3.0.2 (<http://www.r-project.org/>), with 'survival',²⁴ 'cmprsk'²² and 'dynpred'²⁵ libraries.

Results

Patients', disease and transplant characteristics at SCT

In total, 3265 MDS or sAML patients with cytogenetic information were reported to the EBMT-database from 1981 to 2012. Of

Table 2. Transplant characteristics of MDS/sAML patients (n=903).

	N. (%)
Donor type	
Matched related	574 (63.6)
Matched unrelated	329 (36.4)
Stem cell source	
PBSC	583 (64.6)
Bone marrow	320 (35.4)
Conditioning*	
Myeloablative	582 (64.5)
Reduced intensity	320 (35.4)
Recipient-donor sex match**	
Female donor for male recipient	164 (18.2)
All other combinations	733 (81.2)
CMV Ig G of recipient and donor***	
Negative/negative	224 (24.8)
Negative/positive	96 (10.6)
Positive/negative	185 (20.5)
Positive/positive	281 (31.1)

*Missing in one patient. **Missing in 6 patients. ***Unknown in 117 patients. RA: refractory anemia; RARS: refractory anemia with ringsideroblasts; RAEB: refractory anemia with excess of blasts; RCMD: refractory cytopenia with multilineage dysplasia; sAML: secondary acute myeloid leukemia; CMML: chronic myelomonocytic leukemia; CR: complete remission; IPSS: International Prognostic Scoring System; PBSC: peripheral blood stem cells; Ig: Immunoglobulin; CMV: cytomegalovirus.

those, 2569 patients had cytogenetic information dated within one year before SCT. Despite the rather short interval from karyotypic information to transplantation in most patients, there might be a number of patients for whom the cytogenetic information has changed during that time. Patients were excluded because of insufficient cytogenetic information for reliable classification into the 5-group IPSS-R classification, missing essential information on follow up after SCT, recent year of SCT (2011-2012), age below 18 years, treatment-related AML, unknown, syngeneic or mismatched donor, or cord blood graft. The remaining patients were included in the study. These patients received SCT for the treatment of MDS or sAML between 1982 and 2010. At time of SCT, 97 (11%) patients had untreated RA/RARS/RCMD, 250 patients (28%) had untreated advanced MDS or AML evolving from MDS, 218 (24%) patients had advanced MDS or sAML in CR, and 227 (25%) patients were not in remission after treatment (in 12% information was not available). Median time between diagnosis and transplant was 6.6 months (range 0.2-359.3 months). Matched related donor SCT was performed in 574 patients (64%), and matched unrelated donor SCT in 329 patients (36%). Bone marrow (35%) or peripheral blood (65%) served as stem cell graft. A total of 582 patients (65%) received myeloablative preparative regimens, whereas a non-myeloablative regimen was given to 320 patients (35%). Details on disease and patients' characteristics, as well as the transplant procedure, are shown in Tables 1 and 2.

Reclassification of 3-group-IPSS into 5-group-IPSS-R cytogenetic classification

According to the 5-group cytogenetic IPSS-R classification 19 (2%) patients had very good risk cytogenetics, 204 (23%) good risk cytogenetics, 438 (48%) intermediate risk cytogenetics, 178 (20%) poor risk cytogenetics, and 64 (7%) very poor risk cytogenetics.

Comparing the 3-group-IPSS cytogenetic classification with the more recent 5-group IPSS-R cytogenetic classification, patients were re-distributed as follows: 9 patients (5%) of the good risk

Table 3. Univariate analysis for RFS, OS, CIR and NRM in MDS and sAML patients. Outcomes at 60 months after SCT are based on Kaplan-Meier estimates for RFS and OS and on Cumulative Incidence estimates for CIR and NRM. P-values are derived from the 2-sided log-ranks test (RFS and OS) and from the Gray test (CIR and NRM), both tests comparing the entire curves up to 60 months.

Variables	N.	%	RFS (%)	OS (%)	CIR (%)	NRM (%)
All patients	903	100	32	36	36	33
Age						
18-40	262	29	35	40	31	34
40-50	186	21	37	41	31	32
50-60	291	32	29	33	39	32
>60	164	18	24	27	44	33
P	-	-	0.050	0.096	0.018	0.819
Disease status at SCT						
RA/RARS/RCMD untreated						
RAEB(t)/sAML/CMML in CR	97	11	54	57	12	34
RAEB(t)/sAML/CMML untreated	218	24	37	41	40	24
RAEB(t)/sAML/CMML not in CR	227	25	34	39	29	38
P	-	-	<0.001	<0.001	<0.001	0.008
3-group IPSS-cytogenetics						
Good	192	21	36	40	29	35
Intermediate	500	55	34	40	36	30
Poor	211	23	21	24	42	37
P	-	-	<0.001	<0.001	0.020	0.076
5-group IPSS-R-cytogenetics						
Very Good	19	2	42	58	30	28
Good	204	23	36	40	30	34
Intermediate	438	49	36	41	34	31
Poor	178	20	22	27	42	36
Very poor	64	7	10	11	56	34
P	-	-	<0.001	<0.001	<0.001	0.588
Donor						
Matched related	574	64	32	37	38	30
Matched unrelated	329	36	30	34	33	37
P	-	-	0.388	0.134	0.197	0.041
Graft						
Bone marrow	320	35	31	35	30	38
Peripheral blood stem cells	583	65	31	37	39	29
P	-	-	0.193	0.109	0.018	0.001
Conditioning						
Myeloablative	582	64	33	38	32	34
Reduced intensity	320	35	29	33	42	29
P	-	-	0.141	0.717	<0.001	0.097
Recipient-donor sex match						
Female donor for male patient	164	18	25	30	32	42
All other combinations	733	81	33	37	37	30
P	-	-	0.095	0.072	0.285	0.005
CMV status (recipient/donor)						
-/-	224	29	34	40	38	28
-/+	96	12	32	37	38	30
+/-	281	36	34	39	35	31
+/+	185	24	33	35	27	39
P	-	-	0.957	0.585	0.161	0.139
Year of SCT						
1982-1999	272	30	33	36	30	37
2000-2006	323	36	30	35	39	30
2007-2010	308	34	17	32	48	35
P	-	-	0.380	0.259	0.05	0.098

OS: overall survival; RFS: relapse-free survival; CIR: cumulative incidence of relapse; NRM: non-relapse mortality; HR: hazard ratio; CR: complete remission; MRD: matched related donor; MUD: matched unrelated donor; SCT: stem cell transplantation; CMV: cytomegalovirus.

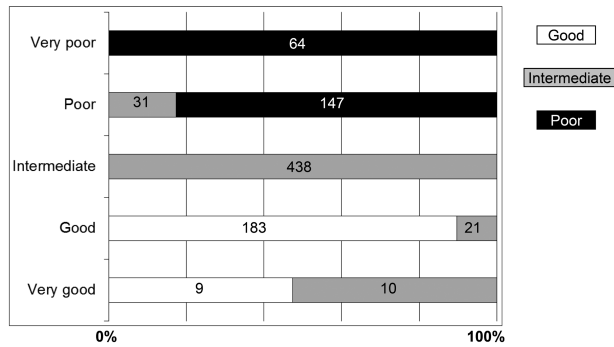


Figure 1. Re-grouping of patients from IPSS cytogenetic subgroups (good/ intermediate/ poor) into new IPSS-R cytogenetic subgroups (very poor/ poor/ intermediate/ good/ very good). Numbers in the diagram indicate absolute numbers of patients.

group became very good risk in the 5-group classification, and 183 patients (95%) remained in the good risk group also in the new classification; the intermediate risk group patients were re-grouped into very good ($n=10$, 2%), good risk ($n=21$, 4%) and poor risk ($n=31$, 6%); 438 patients (88%) remained in the intermediate risk group; 64 patients (44%) of the poor risk group were re-grouped into the very poor risk group according to the new classification; this was proportionally the largest shift within all risk groups (Figure 1).

Outcome analysis

The primary goal of this analysis was to determine RFS after SCT according to the recent 5-group IPSS-R cytogenetic classification and to investigate the added value of the new classification compared to the old for predicting this outcome. We hypothesized that what has been shown for cytogenetic risk profiles and outcome of MDS patients not undergoing SCT¹⁷ in terms of disease progression is also true for transplant patients at time of SCT.

Univariate analysis

Median follow up of patients alive was 60 months after SCT (taking into account artificial censoring at 60 months). The estimated 5-year RFS in all patients was 32%. 5-group cytogenetic IPSS-R information was found to be significantly associated with RFS in univariate analysis ($P<0.001$). RFS was 42% in very good and 36% in good risk patients, 36% in intermediate, 22% in poor and 10% in very poor risk patients at 5 years (Figure 2A).

Since relapse after transplantation is frequently fatal because of limited treatment options, this directly affects OS, which is the secondary end point of our analysis. OS in all patients was 36% at five years after SCT. As expected, 5-group IPSS-R cytogenetic information was also strongly associated with OS (OS: log rank test $P<0.001$). The OS in very good risk patients was 58%, 40% in good risk, 41% in intermediate, 27% in poor and 11% in very poor risk patients after five years (Figure 2B).

Disease status at SCT (RA/RARS/RCMD no pre-treatment; RAEB(t)/sAML/CMML in CR; RAEB(t)/sAML/CMML not in CR, RAEB(t)/sAML/CMML untreated) was a predictor for RFS and OS (OS: $P<0.001$, RFS: $P<0.001$). Higher patient age was predictive for lower RFS ($P=0.05$), but not for OS ($P=0.09$) in univariate analyses. Furthermore, the year of SCT was not associated with RFS ($P=0.38$) or OS ($P=0.26$).

Whether a matched donor was related or unrelated did not significantly affect either RFS ($P=0.39$) or OS ($P=0.13$). Similarly, the donor graft, bone marrow or peripheral blood stem cells, did not

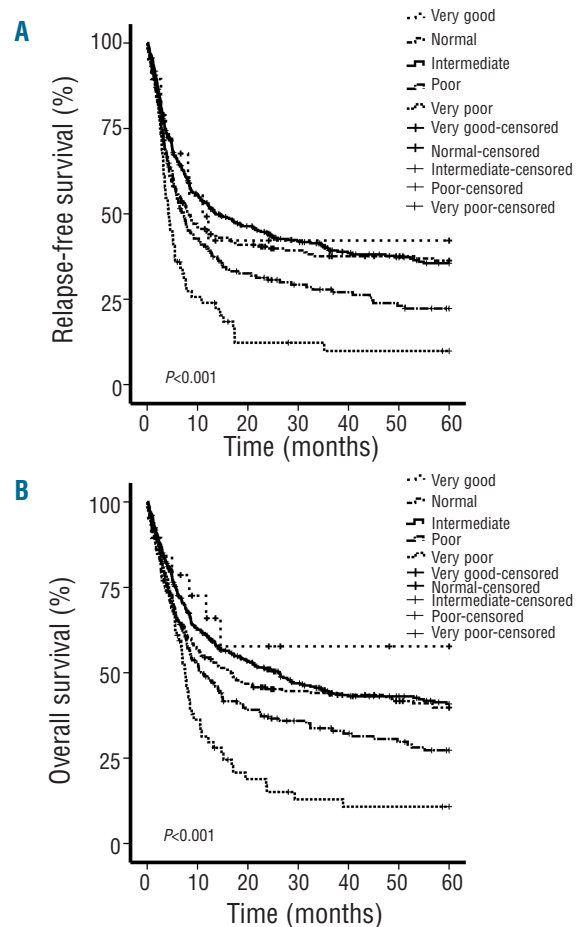


Figure 2. Kaplan-Meier curves of relapse-free (A) and overall (B) survival of MDS/sAML patients after allogeneic stem cell transplantation according to 5-group cytogenetic risk classification.

influence RFS or OS in this cohort of patients (RFS $P=0.19$, OS $P=0.11$), neither did the conditioning regimen (RFS $P=0.14$, OS $P=0.72$). The combination of CMV status of patients and donors (RFS $P=0.96$, OS $P=0.59$) or a female donor for a male recipient (RFS $P=0.09$, OS $P=0.07$) were not significant predictors for RFS or OS in univariate analysis. The type of conditioning regimen (reduced or standard) did not significantly affect outcome (RFS $P=0.14$, OS $P=0.72$) (Table 3).

Multivariate analysis

The goal of the multivariate analysis was to identify the risk factors with best predictive value for RFS and OS with a focus on cytogenetic information. We first built models for RFS and OS including potentially relevant predictors on the basis of results from the literature but excluding cytogenetics (Online Supplementary Table S1). The most predictive variables were selected by means of a back-step selection procedure (excluding covariates associated with $P>0.1$ in the conditional statistic). The proportionality assumption was checked for all variables in this reduced model. The model was then extended by adding the 3-group IPSS-cytogenetic classification as a relevant predictor for outcome. Since the Hazard Ratio for intermediate risk patients in the 3-group IPSS model (with respect to good risk patients) was close to 1 (data not shown), the model was simplified by combining good

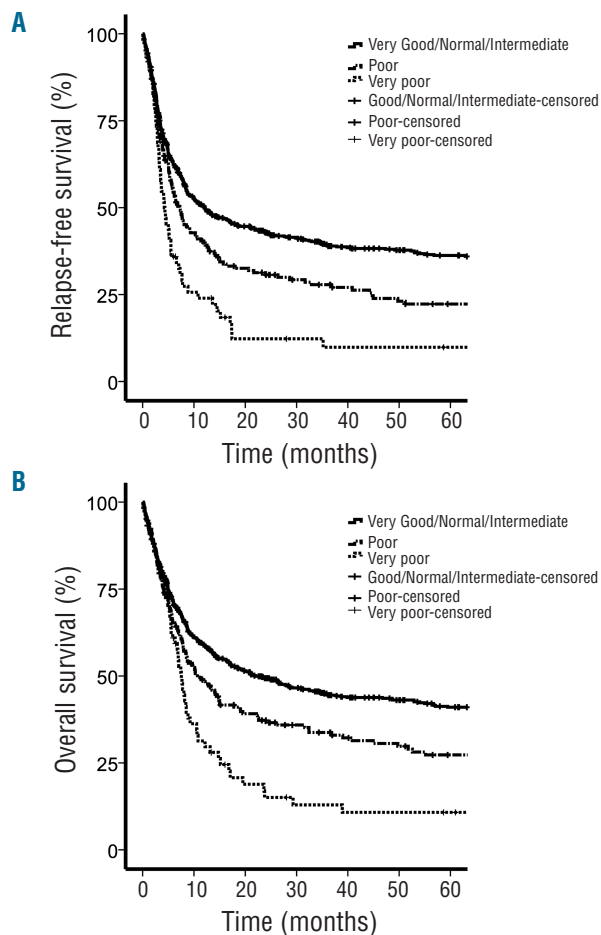


Figure 3. Kaplan-Meier curves of relapse-free (A) and overall (B) survival of MDS/sAML patients after allogeneic stem cell transplantation according to the simplified 5-group cytogenetic risk classification.

and intermediate risk patients into one “standard-group” category (*Online Supplementary Table S2*).

To test whether the recent 5-group cytogenetic classification is most predictive for outcome, we replaced the simplified 3-group cytogenetic with the 5-group IPSS-R-classification in a fourth Cox regression model (*data not shown*). Similarly to what we observed for the 3-group IPSS-classification in the second model, the HRs for good risk patients and for intermediate risk patients (both with respect to very good risk patients) were close to 1. Therefore, the model was simplified by combining very good, good and intermediate risk patients into one “standard-group” category. A comparison of these two models by means of AIC and the cross-validated log partial likelihood showed that the simplified model had better model fit and predictive performance. Patients with poor risk (RFS: HR=1.40; OS: HR=1.38) or very poor risk cytogenetic category (RFS: HR=2.14; OS: HR=2.14) had worse RFS and OS than patients in the other (merged) standard group (Table 4). It is worthy of note that an additional Cox model showed that T-cell depletion during conditioning therapy did not significantly increase relapse risk (*data not shown*).

When comparing the predictive performance of all five models (1=risk factors without cytogenetic information, 2=+3-group IPSS-cytogenetic classification, 3=+simplified 3-group IPSS-cytogenetic classification, 4=+5-group-IPSS-R-cytogenetic classification,

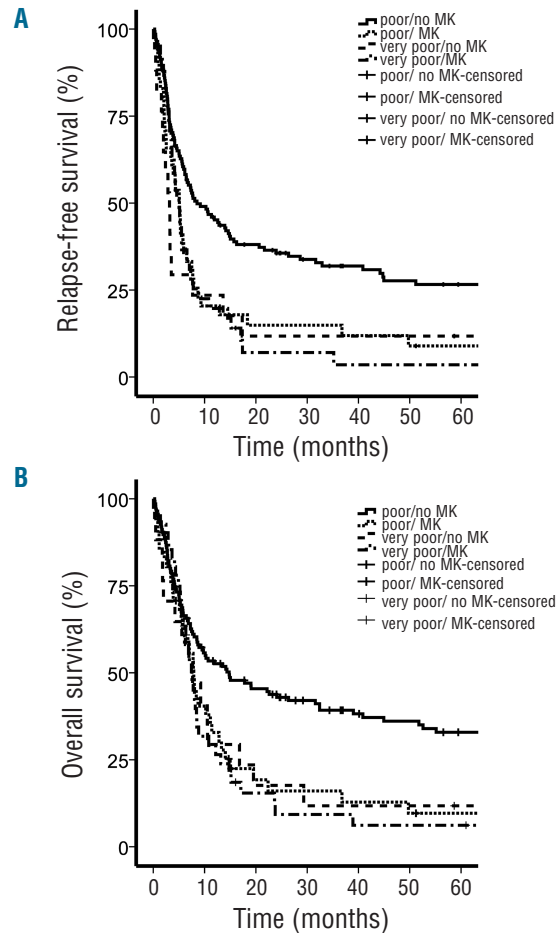


Figure 4. Kaplan-Meier curves of relapse-free (A) and overall (B) survival of MDS/sAML patients with poor and very poor cytogenetic risk with and without monosomal karyotype (MK).

5=+simplified 5-group-IPSS-R cytogenetic classification) both for RFS and OS, according to AIC and cross-validated log partial likelihood, the model with simplified 5-group IPSS-R risk classification performed best for predicting outcomes after SCT. AIC scores for the RFS models were 7261.3, 7245.5, 7243.5, 7240.0, 7236.1, respectively. This shows that the new classification improves outcome prediction for patients at SCT (Figure 3).

Impact of monosomal karyotype

Next, we analyzed the value of MK as a predictor for RFS and OS. In the multivariate models, the presence of MK did not improve the prediction of RFS or OS (*Online Supplementary Table S3*). Since most patients who harbor MK are grouped into the poor and very poor risk cytogenetic IPSS-R classification, we performed a subgroup analysis of these patients, categorizing them into 4 groups based on MK *versus* no MK and very poor *versus* poor risk. Interestingly, MK has an additional impact on prediction of RFS ($P<0.001$) and OS ($P=0.001$), but only in the poor risk group (RFS: $P=0.003$; OS: $P=0.004$; log rank test for poor risk patients only) but not in the very poor risk group (RFS: $P=0.61$; OS: $P=0.71$, log rank test for poor risk patients only). RFS at five years was 27% in poor risk patients without MK and only 9% in poor risk patients with MK. In patients of the very poor risk group the RFS was 12% without and 4% with MK at five years (Figure 4).

Table 4. Cox regression models with simplified 5-group IPSS-R cytogenetic classification for RFS and OS in MDS and sAML patients.

	HR	RFS 95% CI	P	HR	OS 95% CI	P
Donor (matched unrelated <i>vs.</i> matched related)	–		–	1.25	1.03-1.52	0.028
Age			0.001			0.002
18-40	1.0		–	1.0		–
40-50*	0.98	0.76-1.25	0.860	1.04	0.80-1.35	0.769
50-60*	1.14	0.91-1.43	0.252	1.23	0.97-1.56	0.083
>60*	1.62	1.24-2.13	<0.001	1.70	1.27-2.25	<0.001
Disease status at SCT**			<0.001			<0.001
RA/RARS/RCMD untreated	1.0		–	1.0		–
RAEB/sAML/CMML in CR*	1.49	1.05-2.11	0.025	1.39	0.97-2.00	0.076
RAEB/sAML/CMML untreated*	1.69	1.20-2.37	0.003	1.60	1.12-2.28	0.010
RAEB/sAML/CMML treated, not in CR*	2.52	1.81-3.52	<0.001	2.30	1.62-3.24	<0.001
5-group IPSS-cytogenetics			<0.00			<0.00
Standard [§]	1.0		–	1.0		–
Poor*	1.40	1.15-1.71	0.001	1.38	1.12-1.70	0.003
Very poor*	2.14	1.60-2.86	<0.001	2.14	1.59-2.87	<0.001
Year of SCT	0.98	0.96-0.99	0.002	0.97	0.95-0.98	<0.001

*Compared to the first group (reference group) listed in each category. **Patients with missing data for disease status at SCT were kept in the analysis by assigning them to a separate category (HRs not shown). [§]Standard: merged very good, good and intermediate risk patients. OS: overall survival; RFS: relapse-free survival; HR: hazard ratio; CI: confidence interval; IPSS: International Prognostic Scoring System; CR: complete remission; SCT: allogeneic stem cell transplantation.

Table 5. Cox regression models for cause-specific hazards for relapse and non-relapse mortality in MDS and sAML patients.

	HR	CIR 95%CI	P	HR	NRM 95%CI	P
Donor (matched unrelated <i>vs.</i> matched related)	0.85	0.65-1.11	0.229	1.48	1.13-1.94	0.005
Age			0.001			0.394
18-40	1.0		–	1.0		–
40-50*	0.99	0.70-1.42	0.971	1.00	0.71-1.41	0.988
50-60*	1.23	0.90-1.70	0.197	1.09	0.79-1.50	0.604
>60*	1.99	1.37-2.90	<0.001	1.37	0.92-2.03	0.117
Disease status at SCT**			<0.001			0.022
RA/RARS/RCMD untreated	1.0		–	1.0		–
RAEB/sAML/CMML in CR*	3.64	1.93-6.86	<0.001	0.76	0.49-1.19	0.235
RAEB/sAML/CMML untreated*	2.84	1.49-5.40	0.001	1.28	0.85-1.93	0.236
RAEB/sAML/CMML treated, not in CR*	6.17	3.31-11.51	<0.001	1.32	0.88-2.00	0.185
5-group IPSS-cytogenetics			<0.001			0.090
Standard [§]	1.0		–	1.0		–
Poor*	1.64	1.24-2.16	0.001	1.19	0.89-1.60	0.232
Very poor*	2.76	1.89-4.02	<0.001	1.60	1.01-2.53	0.046
Year of SCT	0.99	0.96-1.01	0.248	0.96	0.94-0.98	<0.001

*Compared to the first group (reference group) listed in each category. **Patients with missing data for disease status at SCT were kept in the analysis by assigning them to a separate category (HRs not shown). [§]Standard: merged very good, good and intermediate risk patients. CIR: cumulative incidence of relapse; NRM: non-relapse mortality; HR: hazard ratio; CI: confidence interval; IPSS: International Prognostic Scoring System; CR: complete remission; SCT: allogeneic stem cell transplantation.

Non-relapse mortality and cumulative incidence of relapse

We evaluated the impact of IPSS-R cytogenetic category on the cumulative incidence of relapse (CIR) and non-relapse mortality (NRM). CIR was significantly higher in patients with poor and very poor risk cytogenetics compared to the “standard-group” (5-year CIR 42% and 56% *vs.* 34%, respectively; $P<0.001$), while NRM was similar in these cytogenetic risk groups (5-year NRM 36% and 34% *vs.* 31%, respectively; $P=0.59$) (Figure 5).

Next, we investigated cause-specific hazards for CIR and NRM in a Cox regression model that included the simplified 5-group IPSS-R cytogenetic classification. In this model, age over 60 years (HR=1.99, $P<0.001$), disease status at SCT (RAEB/sAML/CMML in CR, HR=3.64, $P<0.001$; RAEB/sAML/CMML untreated, HR=2.84, $P=0.001$; RAEB/sAML/CMML treated not in CR,

HR=6.17, $P<0.001$), poor (HR=1.64, $P=0.001$) and very poor (HR=2.76, $P<0.001$) cytogenetic risk classification were adverse risk factors for relapse. The very poor risk cytogenetic group was also associated with a high NRM (HR=1.60, $P=0.046$) (Table 5).

Outcome of re-classified patients

Finally, we compared the outcome of re-classified patients. Patients from the IPSS poor risk cytogenetic group distributed into poor (n=147) and very poor (n=64) IPSS-R cytogenetic risk groups. Thirty-one patients from the IPSS-intermediate risk group re-distributed into the poor risk IPSS-R-cytogenetic risk category (Figure 1). The outcome of re-classified very poor risk (from the IPSS poor risk group) and poor risk patients (from IPSS intermediate risk group) was very similar (RFS, $P=0.35$; OS, $P=0.14$), but worse than for the other patients in the IPSS-R poor risk group (RFS, $P=0.011$;

OS, $P=0.026$). The RFS at five years of the patients re-classified from intermediate to poor was 6% and the OS was 13%. Interestingly, of those 31 patients who were re-classified from IPSS intermediate cytogenetic risk group into the poor risk group of the IPSS-R-cytogenetic classification, 30 patients harbored a chromosome 3 aberration (*data not shown*).

Discussion

In this large, international, multicenter study, we clearly show that the recent 5-group cytogenetic IPSS-R classification added value in the prediction of patient outcome after SCT in MDS and sAML patients compared to prediction models with only traditional risk factors or the 3-group IPSS-cytogenetic classification. Patients with poor risk (RFS: HR=1.40; OS: HR=1.38) or very poor risk cytogenetic category (RFS: HR=2.14; OS: HR=2.14) had worse RFS and OS than patients in the other (merged) three risk groups. Interestingly, MK is an additional negative predictor for outcome within patients of the poor, but not the very poor risk group of the 5-group classification. Furthermore, age over 60 years and advanced disease stages (RAEB(t)/sAML/CMML in CR, RAEB(t)/sAML/CMML untreated and RAEB(t)/sAML/CMML not in CR) were significant negative predictors for RFS and OS when statistically tested in multivariate analyses in this retrospective EBMT registry study.

These results are in line with previous reports showing an independent association of the status of the disease^{6,7} and patient age³ with outcome after SCT. The cytogenetic information of the disease had been shown earlier to be a predictor of relapse or disease progression in patients with MDS and sAML undergoing^{10-14,26} or not undergoing^{27,28} SCT.

However, the main focus of this study was to analyze the impact of cytogenetic information using the 5-group cytogenetic IPSS-R information on RFS after SCT, since this information is of major importance in defining post-transplant strategies for the prevention of relapse. Nowadays, several post-transplant strategies are available to handle impending disease relapse. Besides accelerated tapering of immunosuppressive therapy and administration of adjuvant donor leukocyte infusions (aDLI) to achieve graft-versus-tumor effects,²⁹ the use of epigenetic modifiers in these patients seems to be a therapeutic option.³⁰

In order to achieve robust results in this study, we included only matched donors (related and unrelated) and only patients receiving either BM or PBSC as a stem cell graft (no cord blood grafts). Due to the lack of high-resolution human leukocyte antigen-typing data in the majority of the cohort, we were only able to report on 6/6 matched donor and recipients pairs. Only in recent years have we been able to report on 10/10 matched donor and recipient pairs. This might lead to heterogeneous groups of analyzed patients and is, therefore, a potential limitation of our study. We were very strict in selecting patients with available cytogenetic information. More than 72% of MDS patients ($n=2373$) reported to the EBMT database were excluded from the study due to insufficient and implausible cytogenetic reports or because of cytogenetic information which was acquired more than one year before SCT.

Interestingly, similar to other studies,^{13,14} we detected a differential prognostic value for RFS and OS after transplantation for very poor and poor risk patients according to the new IPSS-R-cytogenetic classification, but in contrast to these, not for very good, good and intermediate risk groups. We checked whether the cytogenetic information influenced the outcome to the same extent comparing lower (RA/RARS/RCMD) with higher MDS stages (RAEB/sAML/CMML) and we could not detect a significant difference (*data not shown*).

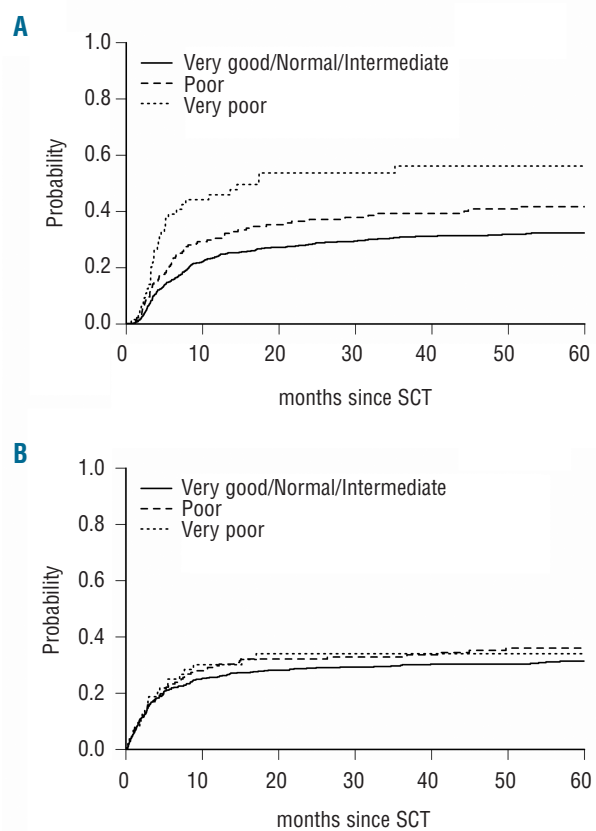


Figure 5. (A) Estimated cumulative incidence of relapse (CIR) and (B) non-relapse mortality (NRM) according to simplified 5-group IPSS-R cytogenetic risk groups until five years after SCT based on competing risks analysis.

We also observed similar results when we used the old IPSS 3-group cytogenetic classification, where only the poor risk group was associated with worse patient outcome after allogeneic transplantation, whereas good and intermediate risk groups had shown no significant difference on survival.

Of note, when comparing the predictive performance of a series of five models both for RFS and for OS, the model with simplified IPSS-R cytogenetics and classical risk factors had the best predictive performance, indicating the distinction between very good, good and intermediate risk patients has no added value in the context of predicting outcome after SCT. Patients in the poor risk (RFS: HR=1.40; OS: HR=1.38) or very poor risk cytogenetic category according to the IPSS-R classification (RFS: HR=2.14; OS: HR=2.14) had worse RFS and OS than patients in the other (merged) standard group (Table 4).

Therefore, the new IPSS-R cytogenetic scoring system improves outcome prediction for MDS/sAML patients after SCT. In contrast to the old 3-group IPSS classification, we can now separate patients not only into two (poor and merged others), but also into three patient groups with clearly different outcomes (very poor, poor and merged others). Additionally we could show that the presence of MK in the poor, but not the very poor risk group predicted worse outcome. Therefore, poor and very poor risk cytogenetic information in combination with MK in patients with MDS or sAML is of major importance for the clinician to decide on post-transplant treatment strategies in terms of immunological or pharmacological interventions.

When we analyzed the patients who were re-grouped from the

old into the new IPSS-R cytogenetic classification we observed that these patients had a rather bad outcome in terms of RFS. We noticed that, especially for the patients re-classifying from the intermediate into the poor risk category, 30 of 31 patients harbored chromosome 3 aberrations. It is known that chromosome 3 aberrations lead to activation of EVI1 expression, which in turn drives leukemogenesis.³¹ One could, therefore, speculate that especially chromosome 3 aberrations enable the underlying disease to escape GvT effects after SCT. Hence, chromosome 3 aberrations are specifically important in the setting of transplantation and new treatment strategies need to be established. In general, somatic mutations such as ASXL1, EVI1 or TP53 in MDS patients might be important predictors for outcome after SCT, similar to what has been shown for patients not undergoing SCT.³²

The predictive value of cytogenetic information for outcome after allogeneic SCT has been reported by others, not only for the 3-group-IPSSclassification,³³ but also for the 5-group IPSS-R-classification.¹³⁻¹⁵ In all studies, unfavorable cytogenetic information, as classified according to the IPSS or IPSS-R classification, predicted worse patient outcome. However, this study is the first to evaluate formally the added value of the 5-group IPSS-R classification compared to the 3-group classification in the setting of SCT for predictive performance and to show that the relevant distinction in categories in this context is standard-poor-very poor when other risk factors are taken into account. Furthermore, all disease-related variables used for outcome prediction are assessed within one year before transplantation and not at first diagnosis of MDS or start of remission-induction chemotherapy, thus avoiding potential bias caused by correlation between timing of assessments and their values. Since our study is to the best of our knowledge the largest study dealing with this topic so far, we were also able to include even a considerable number of very good risk patients. Due to the multinational character of this study, center effects, which occur due to differences in clinical practice, are expected to be well balanced.

To gain information on the best transplant strategy in patients

with different cytogenetic risk groups, we compared outcome of each single IPSS-R-cytogenetic risk group in relation to reduced or standard conditioning (*data not shown*). In this analysis, we could not detect a benefit of one of the two conditioning strategies for any of the risk groups. Similarly, we could not detect any difference regarding RFS or OS in relation to T-cell depleting treatment during conditioning therapy. However, and this is a clear weakness of this retrospective registry based study, we had no complete information on co-morbidities in most patients. It is rather clear that the clinicians' choice for the conditioning regimen frequently depends on these co-morbidities, and only in younger patients with few or no co-morbidities on the disease characteristics. Therefore, this result has to be taken with caution.

In conclusion, this study clearly shows that poor and very poor risk cytogenetic characteristics independently predicted worse patient outcome after SCT in MDS and sAML patients. The presence of MK within the poor risk group of patients gives additional information regarding outcome. Pre- and post-transplant strategies to prevent relapse after allogeneic transplantation in these groups of patients are of major importance.

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