Contribution of Revised International Prognostic Scoring System Cytogenetics to Predict Outcome After Allogeneic Stem Cell Transplantation for Myelodysplastic Syndromes

A Study From the French Society of Bone Marrow Transplantation and Cellular Therapy

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Background. The prognosis of myelodysplastic syndromes (MDS) after allogeneic stem cell transplantation is critically determined by cytogenetic abnormalities, as previously defined by International Prognostic Scoring System (IPSS) cytogenetics. It has been shown that a new cytogenetic classification, included in the IPSS-R (cytogenetic-IPSS-R [C-IPSS-R]), can better predict the outcome of untreated MDS patients. **Methods.** In this study, we assessed the impact of the IPSS-R cytogenetic score (C-IPSS-R) on the outcome of 367 MDS patients transplanted from HLA-identical siblings or HLA allele-matched unrelated donors. **Results.** According to the C-IPSS-R, 178 patients (48%) fell in the good risk, 102 (28%) in the intermediate risk, 77 (21%) in the poor risk, and 10 (3%) in the very poor risk group. In multivariate analysis, after a median follow-up of 4 years, the poor and very poor-risk categories correlated with shorter overall survival (OS) (4-year OS, 32%; hazard ratio [HR], 1.59; $P = 0.009$ and OS, 10%; HR, 3.18; $P = 0.002$, respectively) and higher cumulative incidence of relapse (CIR) (CIR, 52%; HR, 1.82; $P = 0.004$ and CIR, 60%; HR, 2.44; $P = 0.060$, respectively). **Conclusions.** Overall, the C-IPSS-R changed the IPSS cytogenetic risk only in 8% of cases but identified a new risk group, the very poor C-IPSS-R category, with dismal outcome after allogeneic stem cell transplantation (10% 4-year OS, 60% 4-year CIR). Posttransplantation maintenance therapy should be investigated in prospective trials for patients with high-risk C-IPSS-R karyotypes.

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Myelodysplastic syndromes form a heterogeneous group of myeloid neoplasms with varying outcomes, mainly influenced by the cytogenetic abnormalities borne by the malignant clone. Common management of myelodysplastic syndrome (MDS) patients comprises best supportive care, hypomethylating agents (HMAs) or induction-type chemotherapy,

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although none of those treatments will prevent ineluctable progression or relapse. Because of its curative potential, allogeneic stem cell transplantation (allo-SCT) remains the best treatment option for MDS patients.[1-4] The International Prognostic Scoring System (IPSS),[5] the revised IPSS (IPSS-R),[6] and the World Health Organization (WHO) classification–based scoring system (WPSS)[7] are presently in use by clinicians to help risk stratification. Besides bone marrow blasts, cytopenias and transfusion requirement for the WHO classification–based scoring system, cytogenetic abnormalities make for the most adverse item in all the aforementioned scores. Several retrospective studies observed a sustained impact of IPSS-poor risk cytogenetics after allo-SCT, isolating patients with an increased risk of relapse.[8] Karyotypic prognostication of MDS patients has been recently refined into a 5-group classification[9] and included in the IPSS-R (C-IPSS-R).[6] In a large retrospective study, Deeg et al[10] observed a more discriminating effect of this new C-IPSS-R classification compared to IPSS cytogenetics to predict poor prognosis after allo-ST. Additionally, the presence of a monosomal karyotype (MK) was associated with poorer outcome, which was also observed in another study carried out by the European Society for Blood and Marrow Transplantation group.[11] Monosomal karyotypes were included as well in a transplantation-risk index recently published by Della Porta et al.[12]

In this retrospective, multicenter study, we evaluated the impact of the C-IPSS-R classification on the outcome of a large cohort of MDS patients undergoing allo-SCT from HLA-identical siblings or 10/10 HLA allele-matched unrelated donors. Moreover, we assessed its contribution when compared to stratification by IPSS cytogenetics and according to the presence of an MK.

MATERIALS AND METHODS

This study was approved by the French Society of Bone Marrow Transplantation and Cell Therapies (SFGM-TC) board and conducted according to the declaration of Helsinki.

Patient and Donor Characteristics

We analyzed 367 consecutive patients with MDS who underwent allo-SCT in 23 French and Belgian centers between January 1999 and December 2009. Morphological classification, according to French-American-British[13] and WHO classifications[14] was documented as a separate variable at initial diagnosis and at time of transplantation. Prior progression was defined as a change of WHO/French-American-British category, regardless of treatment, between diagnosis and transplant. Disease status at transplant was defined by 2 categories: "active disease" and "responders." The "active disease" group was attributed in the following cases: stable disease, relapse after complete or partial remission, response failure or progressive disease after treatment according to International Working Group 2006 criteria.[15] In addition, patients who received best supportive care only before transplantation were also included in the "active disease" group. When complete or partial remission International Working Group 2006 criteria were observed at transplant, patients were classified as "responders." Patient characteristics at diagnosis and at transplant are summarized in Table 1 and Table 2, respectively.

Transplantation and Follow-Up Modalities

Transplantation modalities were made as homogenous as possible using the following inclusion/exclusion criteria: (i) Patients older than 18 years referred for first allo-SCT. (ii) Source of stem cell was marrow or blood from either a sibling or an HLA-A, –B, –Cw, –DR, and -DQ identical unrelated donor at allele level (so-called 10/10). Patients who received allo-SCT from an HLA-mismatched donor, cord blood, or T-cell–depleted graft, and patients with chronic myelo-monocytic leukemia were excluded. The participating centers were asked to verify the data recorded for each patient in the French Bone Marrow Transplantation Registry and to provide additional information. Quality of the data was controlled using a computerized search for discrepancy errors and vigorous on-site data verification of each file.

TABLE 1.

Baseline characteristics of patients at diagnosis

			C-IPSS-R categories							
			Good		Intermediate		Poor		Very poor	
Patients characteristics	Total (n = 367)	%	n	%	n	%	n	%	n	%
Sex										
Male	230	63	122	68	54	53	50	65	4	40
Female	137	37	56	32	48	47	27	35	6	60
FAB/WHO										
RA/RARS/RCMD/5q-	114	31	50	28	41	40	22	29	1	10
RAEB-1	102	28	49	28	32	31	18	23	3	30
RAEB-2	134	36	70	39	27	27	32	42	5	50
RAEB-t/AML	17	5	9	5	2	2	5	6	1	10
IPSS cytogenetics										
Good	176	48	176	98	0	0	0	0	0	0
Intermediate	96	26	2	2	90	88	4	5	0	0
Poor	95	26	0	0	12	12	73	95	10	100
Monosomal karyotype										
No	304	83	177	99	94	92	31	40	2	20
Yes	63	17	1	1	8	8	46	60	8	80

RARS, RA with ringed sideroblasts; RAEB-T/AML, RAEB in transformation/ acute myeloid leukemia

TABLE 2.

Baseline characteristics of patients at transplantation

			C-IPSS-R categories							
			Good		Intermediate		Poor		Very poor	
Characteristics at transplant	No. patients (n = 367)	%	n	%	n	%	n	%	N	%
Patient age, y										
< 54	184	50	85	48	49	48	44	57	6	60
≥ 54	183	50	93	52	53	52	33	43	4	40
Previous progression										
No	249	68	120	67	70	69	53	69	6	60
Yes	118	32	58	33	32	31	24	31	4	40
Previous treatment										
Best supportive care	146	40	66	37	40	39	37	48	3	30
HMA	42	11	19	11	9	9	12	16	2	20
ITC	151	41	81	45	40	39	25	32	5	50
HMA + ITC	14	4	8	5	5	5	1	1	0	0
Missing data	14	4	4	2	8	8	2	3	0	0
Hb, g/dL										
≥ 9.7	180	49	83	47	48	47	44	57	5	50
< 9.7	177	48	91	51	50	49	32	42	4	40
Missing data	10	3	4	2	4	4	1	1	1	10
Platelets, G/L										
≥ 73	179	49	89	50	51	50	33	43	6	60
< 73	178	48	85	48	47	46	43	56	3	30
Missing data	10	3	4	2	4	4	1	1	1	10
Leukocytes, G/L										
≥ 2.9	182	50	86	48	59	58	34	45	3	30
< 2.9	175	48	88	50	39	38	42	54	6	60
Missing data	10	2	4	2	4	4	1	1	1	10
Time to transplantation, mo										
< 10	184	50	76	43	53	52	45	58	10	100
≥ 10	183	50	102	57	49	48	32	42	0	0
Marrow blasts, %										
< 5	208	57	103	58	61	60	40	52	4	40
≥ 5	159	43	75	42	41	40	37	48	6	60
Disease status[a]										
Responders	158	43	87	49	39	38	27	35	5	50
Active disease	209	57	91	51	63	62	50	65	5	50
Sex mismatch[b]										
Yes	84	23	54	30	14	14	15	19	1	10
No	283	77	124	70	88	86	62	81	9	90
Donor type										
Sibling	229	62	105	59	69	68	48	62	7	70
HLA-matched unrelated	138	38	73	41	33	32	29	38	3	30
Stem cell source										
Marrow	117	32	58	33	29	28	28	36	2	20
PBSC	250	68	120	67	73	72	49	64	8	80
Conditioning										
MAC	141	38	63	35	42	41	32	42	4	40
RIC/NMA	226	62	115	65	60	59	45	58	6	60
ATG										
No	207	56	98	55	60	59	41	53	8	80
Yes	160	44	80	45	42	41	36	47	2	20
TBI										
No	236	64	111	62	67	66	53	69	5	50
Yes	131	36	67	38	35	34	24	31	5	50

[a] Disease status at transplant was defined by two categories: "active disease" and "responders". The "active disease" group was attributed in the following cases: stable disease, relapse after complete or partial remission, response failure or progressive disease after treatment according to IWG 2006 criteria.

[b] Sex mismatch is defined as male patient who received graft from a female donor.

PBSC, peripheral blood stem cells; RIC/NMA, reduced intensity conditioning/nonmyeloablative; ATG, antithymocyte globulin; TBI, total body irradiation; ITC, induction-type chemotherapy.

The HLA matching was crosschecked with the data of the French Bone Marrow Donor Registry as previously described.[16] Predonation work-ups in donors[17] and follow-up after transplantation[18-20] were conducted according to the SFGM-TC guidelines.[21]

Cytogenetics

Cytogenetic analysis at diagnosis was performed using conventional procedures and documented with respect to the International System for Human Cytogenetic Nomenclature. Cytogenetic abnormalities were classified according to the C-IPSS-R classification designed by Shantz et al[5] as well as the IPSS cytogenetic classification. The presence of an MK was also assessed and defined as the combination of 2 monosomies or 1 structural abnormality associated with 1 monosomy.[22] Three patients who fell in the very good risk category were removed from the analysis, and 49 patients were excluded because their files lacked or provided incomplete cytogenetic data.

Statistical Analysis

The analysis was performed on the reference date of April 1, 2011. Overall survival (OS) was defined as the interval from allo-SCT to death, regardless of the cause of death. Relapse was defined as the presence of more than 5% marrow blasts and/or reappearance of major myelodysplastic features associated with cytopenia and evidence of autologous reconstitution when chimerism was available. Nonrelapse mortality (NRM) was defined as death resulting from the graft procedure without evidence of relapse. All censored criteria were calculated from the time of transplantation. Distributions over time were estimated by the Kaplan-Meier product limit method. The log-rank test was used to determine the prognostic value of patient characteristics at transplant on OS. The occurrence of relapse and NRM was studied using a competing risk methodology. For the event of relapse, NRM was considered as the competing event. For NRM, the competing event was relapse. The cumulative incidence of each event was estimated using the Kalbfleish and Prentice method. The individual prognostic value of each variable was assessed by the Gray test (comparison of cumulative incidence curves using bivariate analyses). Variables having a significance level of P less than 0.15 in univariate analysis were introduced in a multivariable Cox regression model for OS, in a Fine and Gray model for relapse and NRM, with backward selection at level P less than 0.15. Adjusted hazard ratios and 95% confidence intervals (95% CI) were computed, and a P value of 0.05 or less was considered statistically significant. Statistical analyses were performed using the SAS and R software programs. The R package "cmprsk" was used for the Fine and Gray model.

RESULTS

Patient Characteristics

At diagnosis, 114 (31%) of the 367 patients had refractory anemia (RA), RA with ringed sideroblasts or refractory cytopenia with multilineage dysplasia, 102 patients (28%) had RA with excess of blasts (RAEB-1 < 10%), 134 patients (36%) had RA with excess of blasts ranging from 10% to 19% (RAEB-2), and 17 patients (5%) had RAEB in transformation/ acute myeloid leukemia with marrow blasts between 20% and 30% (Tables 1 and 2).

We analyzed 230 males (63%) and 137 females (37%) with a median age of 54 years (range, 20-70) at allo-SCT. The donor was an HLA-matched sibling in 229 cases (62%) and an HLA-matched unrelated donor in 138 (38%). The conditioning regimen was myeloablative conditioning (MAC) in 141 patients (38%) and reduced intensity conditioning/ nonmyeloablative in 226 patients (62%).[23] Peripheral blood stem cell was used in 68% and bone marrow stem cells in 32% of our patients. An excess of blasts in the marrow was observed in 159 patients (43%) of our patients. Overall, 118 of the 367 patients (32%) had progressed to more advanced disease before transplantation. A best supportive care approach had been offered to 146 patients (40%), whereas 237 patients (56%) had received either an HMA and/or induction-type chemotherapy. Median time to transplantation was 10 months and median follow-up after transplantation was 4 years (range, 3-142 months). In the poor IPSS karyotypes and intermediate risk C-IPSS-R subsets, median follow-up was of 69 months (range, 18-124) and 53 months (range, 3-134), respectively. The whole estimate for OS was of 45%, whereas cumulative incidence of relapse (CIR) and NRM were of 37% and 24%, respectively. Median time for neutrophil engraftment was of 17 days (range, 0-100). Grade 2 to 4 acute Graft Versus Host Disease (GVHD) was diagnosed in 142 patients (39%) and grade 3 to 4 acute GVHD in 66 patients (18%). Among the 322 patients alive after day 100, we observed chronic GVHD in 176 patients (55%) and extensive GVHD in 67 patients (33%).

Cytogenetic Subgroups

Cytogenetic risk was, according to the C-IPSS-R, good, intermediate, poor, or very poor in 178 (48%), 102 (28%), 77 (21%), and 10 (3%) patients, respectively. The IPSS cytogenetic good risk group coincided completely with the C-IPSS-R good risk group (175 patients). Three patients in the IPSS intermediate risk group were classified as good risk by the C-IPSS-R classification and in those patients the following abnormalities were found: del 12p, del 5q with monosomy 11, del 5q with trisomy 21. Four patients with intermediate IPSS karyotypes fell in the C-IPSS-R poor risk group (all 4 patients carried chromosome 3 abnormalities). The IPSS high-risk patients were split into the IPSS-R intermediate (12 patients with del 7q), poor (73 patients), and very poor risk group (10 patients with complex karyotypes including more than 3 abnormalities). Overall, a change in the cytogenetic risk was only observed in 29 patients (8%).

We observed a MK in 63 (17%) patients. Considering C-IPSS-R, MKs were present in 1 (1%), 8 (8%), 46 (60%), and 8 (80%) patients within the good, intermediate, poor, and very poor risk groups, respectively. Among patients without an MK (n = 304) 177 (58%) fell in the good risk, 94 (31%) in the intermediate risk, 31 (10%) in the poor risk, and 2 (0.6%) in the very poor risk C-IPSS-R category. In those 2 patients, a complex karyotype with more than 3 abnormalities was found but without any monosomy. The following MKs were identified in patients with intermediate risk by C-IPSS-R (n = 8): monosomy 5 and trisomy 21, del 11q and monosomy 20, monosomy 5 and t(X;1), monosomy 5 and trisomy 8 in 2 patients, monosomy 9 and monosomy 11, monosomy 2 and trisomy 17, monosomy 5 and monosomy 11.

TABLE 3.

Univariate analysis

	No. patients	4-y OS		4-y CIR		4-y NRM	
Patient characteristics	**367**	**%**	***P*[a]**	**%**	***P*[b]**	**%**	***P*[b]**
Patient age at transplantation, y							
< 54	184	47	0.345	31	0.019	26	0.431
≥ 54	183	43		41		22	
Sex							
Male	230	43	0.294	36	0.923	26	0.270
Female	137	48		37		20	
FAB/WHO at diagnosis							
RA/RARS/RCMD/5q-	114	50	0.54	33	0.287	24	0.518
RAEB-1	102	41		33		29	
RAEB-2	134	44		42		19	
RAEB-t/AML	17	41		35		24	
RIPSS cytogenetics at diagnosis							
Good	178	53	0.004	32	0.001	21	0.163
Intermediate	102	44		30		31	
Poor	77	32		52		19	
Very poor	10	10		60		30	
IPSS cytogenetics at diagnosis							
Good	176	52	0.015	32	0.004	21	0.139
Intermediate	96	45		31		31	
Poor	95	32		50		21	
Monosomal karyotype at diagnosis							
No	304	48	0.006	32	<0.001	25	0.235
Yes	63	29		60		17	
Previous progression							
No	249	47	0.037	35	0.229	22	0.316
Yes	118	40		40		26	
Previous treatment							
Best supportive care	146	46	0.297	36	0.206	12	0.058
HMA	42	57		41		22	
ITC	151	42		36		29	
HMA + ITC	14	43		34		26	
Missing data	14						
Marrow blasts at transplantation, %							
< 5	208	50	0.012	31	0.013	24	0,834
≥ 5	159	38		44		24	
Disease status at transplantation[c]							
Responders	158	51	0.093	36	0.859	18	0.040
Active disease	209	40		37		28	
Sex mismatch[d]							
Yes	84	46	0.835	33	0.467	26	0.616
No	283	44		37		23	
Donor type							
Sibling	229	47	0.075	39	0.371	21	0.046
HLA-matched unrelated	138	41		33		29	
Stem cell source							
Marrow	117	38	0.219	37	0.531	30	0.060
PBSC	250	48		36		21	
Conditioning							
MAC	141	42	0.413	30	0.006	33	<0,001
RIC	226	47		41		18	
ATG							
No	207	39	0.088	35	0.158	29	0.005
Yes	160	52		39		16	

Continued next page

TABLE 3. (Continued)

Patient characteristics	No. patients 367	4-y OS %	4-y OS P^a	4-y CIR %	4-y CIR P^b	4-y NRM %	4-y NRM P^b
TBI							
No	236	51	0.006	35	0.505	20	0.066
Yes	131	34		40		30	
Hb at transplantation, g/dL							
≥ 9.7	180	49	0.125	37	0.781	27	0.166
< 9.7	177	41		35		19	
Missing data	10						
Platelets at transplantation, G/L							
≥ 73	179	52	0.002	37	0.635	28	0.072
< 73	178	39		35		19	
Missing data	10						
Leukocytes at transplantation, G/L							
≥ 2.9	182	49	0.111	35	0.810	26	0.303
< 2.9	175	42		37		21	
Missing data	10						

[a] Log-Rank.
[b] Gray test (cumulative incidence).
[c] Disease status at transplant was defined by two categories: "active disease" and "responders". The "active disease" group was attributed in the following cases: stable disease, relapse after complete or partial remission, response failure or progressive disease after treatment according to International Working Group 2006 criteria.
[d] Sex mismatch is defined as male patient who received graft from a female donor.
RCMD, refractory cytopenia with multilineage dysplasia.

Univariate Analysis

As shown in Table 3, classification by C-IPSS-R, IPSS cytogenetics and MKs significantly impacted OS and relapse. The OS and CIR according to C-IPSS-R categories are represented in Figure 1.

Overall Survival

The C-IPSS-R ($P = 0.004$), the IPSS ($P = 0.015$) cytogenetic classification, and the presence of an MK ($P = 0.006$) were associated with shorter survival. Previous progression ($P = 0.037$), marrow blasts that are 5% or higher ($P = 0.012$), total body irradiation ($P = 0.006$), and platelet count of 73G/L or less at transplant ($P = 0.002$) also adversely impacted OS.

Cumulative Incidence of Relapse

Patient age ($P = 0.019$), C-IPSS-R ($P = 0.001$), IPSS cytogenetics ($P = 0.004$), MKs ($P < 0.001$), marrow blasts that are 5% or higher ($P = 0.013$) and reduced intensity conditioning/nonmyeloablative ($P = 0.006$) were associated with higher CIR.

Nonrelapse Mortality

Higher NRM was observed in patients with active disease at transplantation ($P = 0.040$) and in those allografted from an unrelated donor ($P = 0.046$). The MAC ($P < 0.001$) and antithymocyte globulin ($P = 0.005$) were also associated with higher NRM.

Subgroups Univariate Analysis

To evaluate the contribution of the C-IPSS-R, we applied this new classification to 95 patients with poor risk IPSS karyotypes and identified 2 groups with different outcomes. As displayed in Figure 2, CIR was significantly lower in patients with intermediate risk C-IPSS-R, compared to a group including both poor and very poor risk C-IPSS-R groups with relapse rates of 17% and 55%, respectively ($P = 0.025$). The C-IPSS-R reclassified a very few patients previously categorized as intermediate risk by IPSS cytogenetics. In this subgroup, 3 patients fell in the good risk category and 4 patients in the poor risk group. No difference was observed regarding relapse rates ($n = 96$, $P = 0.402$).

As shown in Figure 3, among 102 patients classified as C-IPSS-R intermediate risk, patients with MKs relapsed more often (63% vs 28%; $P = 0.006$) but had similar OS rates (29% vs 45%; $P = 0.282$). A trend toward higher relapse rates was also observed in C-IPSS-R poor risk patients with MKs ($n = 77$) but this did not reach statistical significance (61% vs 39%; $P = 0.091$, data not shown).

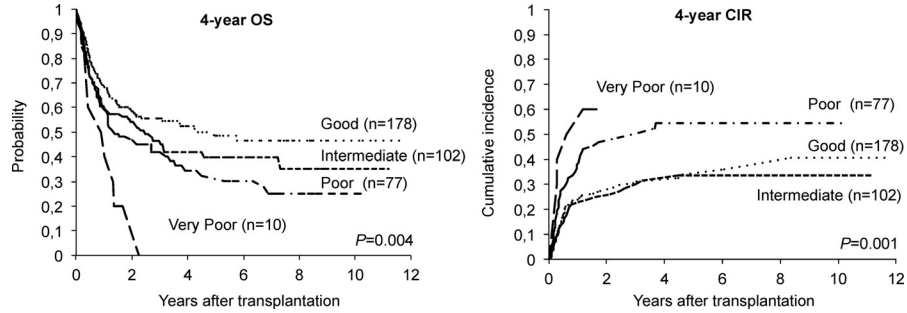

FIGURE 1. Outcome after transplantation according to the C-IPSS-R.

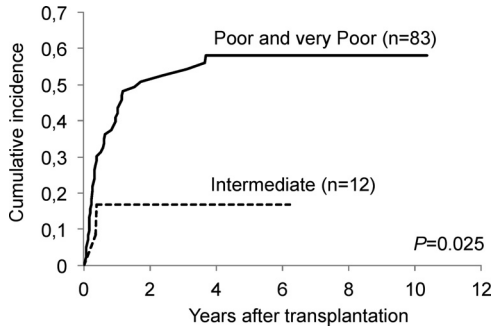

FIGURE 2. Relapse in poor IPSS karyotypes reclassified by the C-IPSS-R.

Multivariate Analysis

Poor and very poor C-IPSS-R groups were independent risk factors for shorter OS (hazard ratio [HR], 1.56; 95% CI, 1.10-2.20; $P = 0.012$ and HR, 2.67; 95% CI, 1.33-5.35; $P = 0.006$, respectively), and higher CIR (HR, 1.82; 95% CI, 1.20-2.72; $P = 0.004$ and HR, 2.44; 95% CI, 0.93-5.27; $P = 0.060$, respectively). Marrow blasts at transplant that are 5% or higher was an independent risk factor for shorter OS (HR, 1.33; 95% CI, 1.00-1.75, $P = 0.049$) and higher CIR (HR, 1.46; 95% CI, 1.04-2.07; $P = 0.034$). Previous progression was associated with shorter OS but without reaching statistical significance (HR, 1.30; 95% CI, 0.97-1.74; $P = 0.081$). Patients who received total body irradiation had significantly shorter OS (HR, 1.38; $P = 0.010$). The MAC was associated with lower relapse rates (HR, 0.59; 95% CI, 0.40-0.85; $P = 0.004$, respectively). Two independent risk factors for higher NRM were identified: HLA-matched unrelated donors (HR, 1.57; 95% CI, 1.03-2.40; $P = 0.035$) and MAC regimens (HR, 2.17; 95% CI, 1.40-3.33, $P < 0.001$) (Table 4).

DISCUSSION

Allo-SCT remains today the only therapeutic option to potentially cure patients suffering from MDS. However, high-risk cytogenetics strongly hinders the procedure. Because the IPSS-R cytogenetic classification was based on analysis of nontransplanted MDS patients, we wished to determine its contribution once compared to other cytogenetic classifications, such as IPSS cytogenetics and MKs. Pretransplant tumor burden, reflected by the percentage of marrow blasts, has been previously linked to adverse outcome[3,24] and was also in our study an independent risk factor for relapse. We took into account that previous therapy influenced the percentage of marrow blasts at transplant and hence considered cytogenetics and marrow blasts separately, as opposed to other authors who studied the IPSS-R as a whole.[12] Although the IPSS-R seems to help the risk-stratification of MDS patients at diagnosis, we find it challenging to use this new classification at the time of allo-SCT. As a matter of fact, the percentage of marrow blasts and cytopenias cannot be interpreted with accuracy at the time of transplant because the alteration of those parameters can result from either the efficacy or toxicity of the treatment administered before transplantation. Indeed, this prognostic tool relies on variables unmodified by therapy and determined specifically at diagnosis.[6]

Because clonal evolution is common in MDS during the course of the disease, cytogenetic evaluation before allo-SCT would be more appropriate. However, only cytogenetic evaluation at diagnosis was considered in our study because of the missing data. Of note, we observed similar results when analyzing cytogenetics at transplant despite the smaller number of patients (data not shown).

The main findings in our study were that patients classified at diagnosis in the C-IPSS-R high-risk categories (poor and very poor risk) experienced higher relapse rates and shorter OS after allo-SCT. These findings are in line with aforementioned studies.[10,12] As expected, we also found an independent impact of poor risk IPSS cytogenetics and MKs on posttransplantation outcomes (data not shown), which has already been reported by others.[8,11]

Because many clinicians still commonly use the IPSS, we investigated how the C-IPSS-R could contribute to more accurate prognostication by changing the cytogenetic risk of our patients. Considering their former IPSS cytogenetic group, a change in prognostic category after applying C-IPSS-R was only observed in 8% of cases. In a study reported by the Seattle group, this percentage was higher (about 17%), in contrast with our study.[10] At first glance, cytogenetic risk only seems to be modified in a small number of patients. Consequently, we took a closer look at the outcome and the specific chromosomal abnormalities observed in these subsets. In patients labeled poor risk according to IPSS cytogenetics, the C-IPSS-R classification distinguished 13 intermediate risk patients with significantly lower relapse rates (Figure 2). Indeed, IPSS cytogenetics overlook the better prognosis associated with isolated del(7q), which was identified in all these IPSS-R intermediate/IPSS poor cytogenetic risk patients. Interestingly, patients with chromosome 3 abnormalities ($n = 4$), which were previously considered as intermediate risk by IPSS, were moved to the poor risk C-IPSS-R group. Besides these observations, a change of cytogenetic risk category after applying the C-IPSS-R was only observed in about 8% of patients compared to their previous IPSS cytogenetic risk. If cytogenetic risk only changed in a few patients, the C-IPSS-R defined a group of patients with very poor outcome, represented by the very poor risk category, with a 60% cumulative incidence of relapse and 10% OS. Unlike what has been previously described,[10,12] a limited number of patients (n = 10) was included in the very poor risk group in our study. The study design could be responsible for this low percentage because we systematically excluded allo-SCT from donor with HLA mismatch. Given the urgent need for

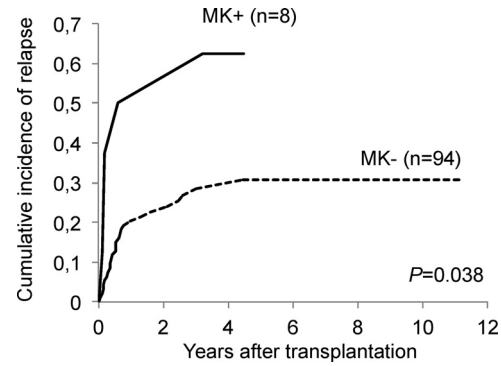

FIGURE 3. Impact of MKs on relapse in the C-IPSS-R intermediate risk group.

TABLE 4.

Multivariate analysis

Characteristics	4-y OS			4-y CIR			4-y NRM		
	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
C-IPSS-R									
Good	1			1					
Intermediate	1.34	0.95-1.87	0.091	0.96	0.61-1.47	0.85			
Poor	1.56	1.10-2.20	0.012	1.82	1.20-2.72	0.004			
Very poor	2.67	1.33-5.35	0.006	2.44	0.93-5.27	0.060			
Previous progression									
No	1	0.97-1.74	0.081						
Yes	1.30								
Marrow blasts at transplantation									
< 5%	1	1.00-1.75	0.049	1	1.04-2.07	0.034			
≥ 5%	1.33			1.46					
TBI									
No	1	1.09-1.92	0.010						
Yes	1.45								
Donor type									
Sibling	1	1.03-2.40	0.035						
HLA-matched unrelated	1.57								
Conditioning									
RIC/NMA				1	0.40-0.85	0.004	1	1.40-3.33	<0.001
MAC				0.59			2.17		

allo-SCT, most patients with very complex karyotypes are more likely to receive such grafts.

In accordance with other studies,[10-12,25] MKs were in our patients a strong risk factor for adverse outcome after allo-SCT. Two independent studies called into question the prognostic value of MKs in cohorts of nontransplanted MDS patients.[26,27] Recently, Kelaidi et al[28] reported similar findings in 98 MDS patients undergoing allo-SCT. They argued that the additional karyotypic abnormalities frequently associated with MKs (such as complex and very complex karyotypes), and not MKs themselves, account for their negative influence on outcome. After multivariate analysis taking into account karyotype complexity, they concluded that MKs do not affect outcome independently. In line with these findings, 86% of MKs (n = 54) in our study were already considered as poor or very poor risk by the C-IPSS-R. Nonetheless, we observed MKs in a small number of patients (n = 8) classified as intermediate risk by the C-IPSS-R, which were at higher risk for relapse (Figure 3) but did not experience significantly shorter survival. We conclude that if MKs are unlikely to refine classification by the C-IPSS-R, their prognostic impact within intermediate IPSS-R karyotypes remains to be investigated in a larger cohort.

Overall, our study confirms the prognostic value of the C-IPSS-R classification in patients with MDS undergoing allo-SCT. Particularly in patients with poor IPSS cytogenetics, this classification is more discriminant and distinguishes a very poor risk group with dismal outcome. How should we manage patients with very poor C-IPSS-R risk? In 2 recent studies published under the aegis of the SFGM-TC group, Damaj et al[16,29] concluded that the absence of cytoreductive therapy (intensive chemotherapy or azacytidine) did not alter outcome after allo-SCT. In addition, Itzykson et al[30] reported that patients with complex karyotypes respond poorly and transiently to azacytidine. In patients fit for the procedure, we therefore encourage early and upfront allo-SCT in patients with very poor C-IPSS-R karyotypes.[31] This approach could be followed by posttransplant preventive strategies, such as HMAs[32,33] and/or donor lymphocyte infusions.[34]

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REFERENCES

1. Jurado M, Deeg HJ, Storer B, et al. Hematopoietic stem cell transplantation for advanced myelodysplastic syndrome after conditioning with busulfan and fractionated total body irradiation is associated with low relapse rate but considerable nonrelapse mortality. *Biol Blood Marrow Transplant*. 2002;8:161–169.
2. Lim Z, Brand R, Martino R, et al. Allogeneic hematopoietic stem-cell transplantation for patients 50 years or older with myelodysplastic syndromes or secondary acute myeloid leukemia. *J Clin Oncol*. 2010;28:405–411.
3. Warlick ED, Cioc A, Defor T, Dolan M, Weisdorf D. Allogeneic stem cell transplantation for adults with myelodysplastic syndromes: importance of pretransplant disease burden. *Biol Blood Marrow Transplant*. 2009;15:30–38.
4. Yakoub-Agha I, de La Salmoniere P, Ribaud P, et al. Allogeneic bone marrow transplantation for therapy-related myelodysplastic syndrome and acute myeloid leukemia: a long-term study of 70 patients-report of the French society of bone marrow transplantation. *J Clin Oncol*. 2000;18:963–971.
5. Greenberg P, Cox C, LeBeau MM, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. *Blood*. 1997;89:2079–2088.
6. Greenberg PL, Tuechler H, Schanz J, et al. Revised international prognostic scoring system for myelodysplastic syndromes. *Blood*. 2012;120:2454–2465.

7. Malcovati L, Germing U, Kuendgen A, et al. Time-dependent prognostic scoring system for predicting survival and leukemic evolution in myelodysplastic syndromes. *J Clin Oncol*. 2007;25:3503–3510.
8. Nevill TJ, Fung HC, Shepherd JD, et al. Cytogenetic abnormalities in primary myelodysplastic syndrome are highly predictive of outcome after allogeneic bone marrow transplantation. *Blood*. 1998;92:1910–1917.
9. Schanz J, Tuchler H, Sole F, et al. New comprehensive cytogenetic scoring system for primary myelodysplastic syndromes (MDS) and oligoblastic acute myeloid leukemia after MDS derived from an international database merge. *J Clin Oncol*. 2012;30:820–829.
10. Deeg HJ, Scott BL, Fang M, et al. Five-group cytogenetic risk classification, monosomal karyotype, and outcome after hematopoietic cell transplantation for MDS or acute leukemia evolving from MDS. *Blood*. 2012;120:1398–1408.
11. van Gelder M, de Wreede LC, Schetelig J, et al. Monosomal karyotype predicts poor survival after allogeneic stem cell transplantation in chromosome 7 abnormal myelodysplastic syndrome and secondary acute myeloid leukemia. *Leukemia*. 2013;27:879–888.
12. Della Porta MG, Alessandrino EP, Bacigalupo A, et al. Predictive factors for the outcome of allogeneic transplantation in patients with myelodysplastic syndrome stratified according to the revised International Prognostic Scoring System (IPSS-R). *Blood*. 2014;123:2333–2342.
13. Bennett JM, Catovsky D, Daniel MT, et al. Proposals for the classification of the acute leukaemias. French-American-British (FAB) co-operative group. *Br J Haematol*. 1976;33:451–458.
14. Swerdlow SH, Campo E, Harris NL, et al. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. Lyon, France: International Agency for Research on Cancer, 2008.
15. Cheson BD, Greenberg PL, Bennett JM, et al. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. *Blood*. 2006;108:419–425.
16. Damaj G, Duhamel A, Robin M, et al. Impact of azacitidine before allogeneic stem-cell transplantation for myelodysplastic syndromes: a study by the Societe Francaise de Greffe de Moelle et de Therapie-Cellulaire and the Groupe-Francophone des Myelodysplasies. *J Clin Oncol*. 2012;30:4533–4540.
17. Dulery R, Giraud C, Beaumont JL, et al. How to handle unexpected biological abnormalities observed in the pre-donation workup for hematopoietic stem cell transplantation: an SFGM-TC report on pre-transplant cytomegalovirus, Epstein-Barr virus, *Toxoplasma gondii*, or syphilis IgM positive serology test. *Pathol Biol (Paris)*. 2013;61:155–157.
18. Bay JO, Peffault de Latour R, Bruno B, et al. [Diagnosis and treatment of CMV and EBV Reactivation as well as Post-transplant Lymphoproliferative Disorders following Allogeneic Stem Cell Transplantation: An SFGM-TC report]. *Pathol Biol (Paris)*. 2013;61:152–154.
19. Deconinck E, Dalle JH, Berceanu A, et al. How I manage respiratory syncytial virus, human herpesvirus 6 and adenovirus reactivation or infection after allogeneic stem cell transplantation: a report of the SFGM-TC. *Pathol Biol (Paris)*. 2013;61:149–151.
20. Belaiche S, Yafour N, Balcaen S, et al. Utilisation of immunosuppressants in the prevention of a graft versus host reaction: Report by the SFGM-TC. *Pathol Biol*. 2014;62:197–203.
21. Yakoub-Agha I. Fourth annual series of workshops of the SFGM-TC to harmonize practices in allogeneic stem cell transplantation. *Pathol Biol (Paris)*. 2014;62(4):197.
22. Breems DA, Van Putten WL, De Greef GE, et al. Monosomal karyotype in acute myeloid leukemia: a better indicator of poor prognosis than a complex karyotype. *J Clin Oncol*. 2008;26:4791–4797.
23. Bacigalupo A, Ballen K, Rizzo D, et al. Defining the intensity of conditioning regimens: working definitions. Biology of blood and marrow transplantation. *Blood Marrow Transplant*. 2009;15:1628–1633.
24. Sierra J, Perez WS, Rozman C, et al. Bone marrow transplantation from HLA-identical siblings as treatment for myelodysplasia. *Blood*. 2002;100:1997–2004.
25. Wudhikarn K, Van Rheeden R, Leopold C, Rattanaumpawan P, Gingrich R, de Magalhaes Silverman M. Outcome of allogeneic stem cell transplantation in myelodysplastic syndrome patients: prognostic implication of monosomal karyotype. *Eur J Haematol*. 2012;89:294–301.
26. Schanz J, Tuchler H, Sole F, et al. Monosomal karyotype in MDS: explaining the poor prognosis? *Leukemia*. 2013;27:1988–1995.
27. Valcarcel D, Adema V, Sole F, et al. Complex, not monosomal, karyotype is the cytogenetic marker of poorest prognosis in patients with primary myelodysplastic syndrome. *J Clin Oncol*. 2013;31:916–922.
28. Kelaidi C, Tzannou I, Baltadakis I, et al. Specific abnormalities versus number of abnormalities and cytogenetic scoring systems for outcome prediction after allogeneic hematopoietic SCT for myelodysplastic syndromes. *Bone Marrow Transplant*. 2014;49:1022–1028.
29. Damaj G, Mohty M, Robin M, et al. Up-front allogeneic stem cell transplantation following reduced intensity/nonmyeloablative for patients with myelodysplastic syndrome. A Study By the Société Française de Greffe de Moelle et de Thérapie Cellulaire (SFGM-TC). *Biol Blood Marrow Transplant*. 2014;20:1349–1355.
30. Itzykson R, Thepot S, Quesnel B, et al. Prognostic factors for response and overall survival in 282 patients with higher-risk myelodysplastic syndromes treated with azacitidine. *Blood*. 2012;117:403–411.
31. Yakoub-Agha I, Deeg J. Are hypomethylating agents replacing induction-type chemotherapy before allogeneic stem cell transplantation in patients with myelodysplastic syndrome? *Biol Blood Marrow Transplant*. 2014;20:1885–1890.
32. de Lima M, Giralt S, Thall PF, et al. Maintenance therapy with low-dose azacitidine after allogeneic hematopoietic stem cell transplantation for recurrent acute myelogenous leukemia or myelodysplastic syndrome: a dose and schedule finding study. *Cancer*. 2010;116:5420–5431.
33. Goodyear OC, Dennis M, Jilani NY, et al. Azacitidine augments expansion of regulatory T cells after allogeneic stem cell transplantation in patients with acute myeloid leukemia (AML). *Blood*. 2012;119:3361–3369.
34. Depil S, Deconinck E, Milpied N, et al. Donor lymphocyte infusion to treat relapse after allogeneic bone marrow transplantation for myelodysplastic syndrome. *Bone Marrow Transplant*. 2004;33:531–534.