Coalesced Multicentric Analysis of 2,351 Patients With Myelodysplastic Syndromes Indicates an Underestimation of Poor-Risk Cytogenetics of Myelodysplastic Syndromes in the International Prognostic Scoring System

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ABSTRACT

Purpose

The International Prognostic Scoring System (IPSS) remains the most commonly used system for risk classification in myelodysplastic syndromes (MDSs). The IPSS gives more weight to blast count than to cytogenetics. However, previous publications suggested that cytogenetics are underweighted in the IPSS. Here we investigate the prognostic impact of cytogenetic subgroups compared with that of bone marrow blast count in a large, multicentric, international patient cohort.

Patients and Methods

In total, 2,351 patients with MDS who have records in the German-Austrian and the MD Anderson Cancer Center databases were included and analyzed in univariate and multivariate models regarding overall survival and risk of transformation to acute myeloid leukemia (AML). The data were analyzed separately for patients treated with supportive care without specific therapy, with AML-like chemotherapy, or with other therapy regimens (low-dose chemotherapy, demethylating agents, immune modulating agents, valproic acid, and cyclosporine).

Results

The prognostic impact of poor-risk cytogenetic findings (as defined by the IPSS classification) on overall survival was as unfavorable as an increased ($> 20\%$) blast count. The hazard ratio (compared with an abnormal karyotype or a bone marrow blast count $< 5\%$) was 3.3 for poor-risk cytogenetics, 4.8 for complex abnormalities harboring chromosomes 5 and/or 7, and 3.1 for a blast count of 21% to 30% ($P < .01$ for all categories). The predictive power of the IPSS cytogenetic subgroups was unaffected by type of therapy given.

Conclusion

The independent prognostic impact of poor-risk cytogenetics on overall survival is equivalent to the impact of high blast counts. This finding should be considered in the upcoming revision of the IPSS.

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INTRODUCTION

Myelodysplastic syndromes (MDSs) constitute a heterogeneous group of clonal stem-cell diseases characterized by hypercellular bone marrow and an increased rate of intramedullary apoptosis, peripheral cytopenias and corresponding clinical symptoms such as anemia, bleeding events, and susceptibility to infections.¹

The clinical course of the disease is highly variable, ranging from stable disease over 10 or more years to death within a few months due to cytopenias or transformation to acute myelogenous leukemia

(AML). To better understand such prognostic differences, various scoring systems have been designed over the past 15 years²⁻⁵ with the International Prognostic Scoring System (IPSS) being the most commonly used.⁶ Derived from data on 816 patients with primary MDS who generally received supportive care only until they progressed to AML, the IPSS is based on the number of peripheral cytopenias, cytogenetics, and percentage of bone marrow blasts. The IPSS considers blast count as most important of these, leading to a higher score for patients with increased blasts than for those with unfavorable cytogenetics.

Table 1. Characteristics of Patient Cohort

Characteristic	German-Austrian Database (n = 988)		MD Anderson Cancer Center Database (n = 1,363)		Total (N = 2,351)	
	No.	%	No.	%	No.	%
Sex*						
Male	547	55.4	919	67.4	1,466	62.4
Female	441	44.6	444	32.6	885	37.6
Age, years*						
Median	65.9		66.0		66.0	
Range	17-91		17-94		17-94	
FAB classification*						
RA/RARS	392	39.7	444	32.6	836	35.6
RAEB	239	24.2	511	37.5	750	31.9
RAEBT	187	18.9	408	25.3	595	25.3
CMML	154	15.6	0	0.0	154	6.6
No FAB classification	16	1.6	0	0.0	16	0.7
WHO classification*						
RA/RARS	29	2.9	31	2.8	60	2.6
RCMD/RCMD-RS	75	7.6	52	3.8	127	5.4
RAEB-1	45	4.6	261	19.1	306	13.0
RAEB-2	83	8.4	447	32.8	530	22.5
CMML	20	2.0	0	0.0	20	0.9
5q- syndrome	13	1.3	5	0.4	18	0.8
AML	28	2.8	211	15.5	239	10.2
No WHO classification	695	70.3	356	26.1	1,051	44.7
Cytogenetic subgroup*						
Normal karyotype	500	50.6	656	48.1	1,156	49.2
Del(5q)	73	7.4	73	5.4	146	6.2
-7/del(7q)	49	5.0	50	3.7	99	4.2
+8	52	5.3	80	5.9	132	5.6
Del(20q)	16	1.6	36	2.6	52	2.2
-Y	25	2.5	17	1.2	42	1.8
Others (noncomplex)	147	14.9	119	8.7	266	11.3
Complex (no chromosome 5 and/or 7 abnormalities)	20	2.0	77	5.6	97	4.1
Complex (chromosome 5 and/or 7 abnormalities)	106	10.7	255	18.7	361	15.4
IPSS cytogenetic risk group*						
Good	614	62.1	782	57.4	1,396	59.4
Intermediate	199	20.1	199	14.6	398	16.9
Poor	175	17.7	382	28.0	557	23.7
Bone marrow blast count, %*						
< 5	404	44.3	492	36.1	896	39.4
5-10	184	20.2	347	25.5	531	23.3
11-20	170	18.6	353	25.9	523	23.0
21-30	154	16.9	171	12.5	325	14.3
Peripheral blood count						
Hemoglobin						
Median	9.3		9.5		9.4	
Range	4-16		4-16		4-16	
ANC						
Median	1.2		1.4		1.4	
Range	0-38		0-75		0-75	
Platelets*						
Median	89		63		69	
Range	3-919		0-1,195		0-1,195	
Therapy*						
Supportive care	603	61.0	689	50.6	1,292	55.0
Intensive chemotherapy	356	36.0	457	33.5	813	34.6
Other therapy	26	2.6	210	15.4	236	10.0
Bone marrow transplantation	3	0.3	7	0.5	10	0.4
Observation time*						
Median	44.2		70.4		57.7	
Range	0.1-241.5		0.1-192.8		0.1-241.5	

Abbreviations: FAB, French-American-British classification criteria; RA, refractory anemia; RARS, refractory anemia with ringed sideroblasts; RAEB, refractory anemia with excess of blasts; RAEBT, refractory anemia with excess of blasts in transformation; CMML, chronic myelomonocytic leukemia; RCMD, refractory cytopenia with multilineage dysplasia; RCMD-RS, RCMD with ringed sideroblasts; AML, acute myeloid leukemia; IPSS, International Prognostic Scoring System; ANC, absolute neutrophil count.

* $P < .05$.

Recently, publications from the Spanish MDS group,⁷ the Italian MDS group,⁸ and the German-Austrian (GA) MDS study group^{9,10} provided some evidence that cytogenetics are underweighted in the IPSS and assigned a higher weight to unfavorable cytogenetics (as defined by the IPSS). Here, we examine the relative prognostic significance of bone marrow blasts and cytogenetics with the goal of informing the planned revision of the IPSS.

PATIENTS AND METHODS

Patients

Clinical and cytogenetic data from 2,351 patients with primary MDS originating from the GA and MD Anderson (MDA) databases were combined and retrospectively analyzed. The GA database includes data from four institutions in Austria (Hanusch-Hospital, Vienna; Elisabethinen Hospital, Linz; Medical University of Vienna, Vienna; and Innsbruck Medical University, Innsbruck) and four institutions in Germany (University of Duesseldorf, Duesseldorf; St. Johannes Hospital, Duisburg; University of Goettingen, Goettingen; and University of Freiburg, Freiburg). Partial results from the GA database have been published previously.^{9,11} The patients were diagnosed between 1972 and 2010 and followed until May 2010. The median observation time was 57.7 months (range, 0.1 to 241.5 months). All patients gave their informed consent to the study. Data concerning the patient cohort are provided in Table 1. The study was conducted in accordance with the modified declaration of Helsinki.

Methods

Only patients with cytomorphologically confirmed diagnosis of MDS according to French-American-British (FAB) classification criteria were included in the study. Patients were excluded if they were younger than age 16 years and had therapy-associated MDS, missing cytogenetic data or an unsuccessful cytogenetic examination, AML (blast count > 30% as defined by the

FAB classification criteria), or lacked information regarding the type of therapy. On the basis of these criteria, 1,396 patients were excluded.

Cytogenetics

Cytogenetic analyses were performed at the individual centers by using standard methods described elsewhere.¹ Karyotypes were described according to the International System for Human Cytogenetics Nomenclature (ISCN),¹² and karyotypes from the GA database were centrally reviewed by J.S., C.S., and D.H. The number of metaphases analyzed ranged from 5 to 194 with a median of 20. Patients with cytogenetics analyzed by using fluorescent in situ hybridization only were not included. The risk stratification of cytogenetic findings was categorized as defined by the IPSS.⁶ Complex ($\geq$ three) abnormalities were divided into two subgroups: complex abnormalities harboring abnormalities of chromosomes 5 and/or 7 versus complex abnormalities without these abnormalities.

Bone Marrow Examinations

Bone marrow examinations were performed at the individual centers by experienced hematologists. All findings were classified according to the FAB classification¹³ and, after the introduction of the WHO classification in 1999,¹⁴ also by the WHO classification in 1,300 of 2,351 patients. For clarity, only the FAB classification is used in this article. U.G., A.G., and C.A reviewed all bone marrow findings in the GA database centrally.

Therapy

Patients receiving different treatment modalities were included in the study (see Results). For statistical analyses, patients were divided into three groups according to the type of therapy given for MDS: (1) supportive care, including blood transfusions, antibiotics, antimycotic agents, iron chelation, hematopoietic growth factors, or amifostine; (2) chemotherapy as would be given for AML; or (3) other types of therapy (low-dose chemotherapy, valproic acid, decitabine or 5-azacytidine, cyclosporine, and lenalidomide or thalidomide). Because of the small number of patients ($n = 10$), those who underwent hematopoietic cell transplantation were excluded from analysis.

Table 2. Univariate and Multivariate Analysis of Overall Survival and AML Transformation in Patients Treated With Supportive Care Exclusively

Category	Overall Survival (months)			AML Transformation (cumulative risk*)				Overall Survival (n = 1,185)		AML Transformation* (n = 1,069)	
	No.	Median	P	No.	1-Year (%)	5-Year (%)	P	HR	95% CI	HR	95% CI
Karyotype			†				‡				
Normal	654	34.5		603	5.6	11.7		1.0	Ref.	1.0	Ref.
Del(5q)	97	43.6		89	4.1	12.0		1.0	0.8 to 1.1	1.0	0.5 to 2.1
-Y	32	50.3		29	0.0	5.6		0.8	0.5 to 1.3	0.6	0.1 to 2.6
Del(20q)	34	33.7		32	7.1	10.7		1.1	0.7 to 1.7	1.3	0.4 to 4.2
+8	66	19.2		56	9.5	15.8		1.8	1.3 to 2.5†	1.6	0.7 to 3.3
Others	137	29.3		120	5.7	14.9		1.1	0.9 to 1.4	1.1	0.6 to 2.0
-7/del(7q)	46	15.8		41	22.5	34.8		1.9	1.3 to 2.7†	3.6	1.9 to 6.7†
Complex (no chromosome 5 and/or 7 abnormalities)	45	9.7		40	6.5	6.5		2.4	1.6 to 3.4†	0.7	0.2 to 2.8
Complex (chromosome 5 and/or 7 abnormalities)	146	5.6		131	12.0	14.5		4.8	3.9 to 6.0†	1.4	0.8 to 2.4
IPSS cytogenetic subgroup			†				N/S				
Good	817	36.6		753	5.2	11.4		1.0	Ref.	1.0	Ref.
Intermediate	203	25.7		176	6.9	15.1		1.3	1.1 to 1.6†	1.2	0.8 to 2.0
Poor	237	7.5		212	13.0	16.8		3.3	2.7 to 3.9†	1.7	1.1 to 2.6†
Bone marrow blast count (%)			†				†				
< 5	648	44.8		597	3.5	9.0		1.0	Ref.	1.0	Ref.
5-10	285	14.4		267	8.4	16.4		2.1	1.8 to 2.6†	2.1	1.4 to 3.3†
11-20	197	15.8		175	10.3	16.5		2.0	1.6 to 2.4†	2.2	1.4 to 3.6†
21-30	102	8.3		86	20.5	23.3		3.1	2.4 to 4.0†	2.9	1.7 to 5.1†

Abbreviations: AML, acute myeloid leukemia; HR, hazard ratio; Ref., reference category; IPSS, International Prognostic Scoring System; N/S, not significant.

*Calculated by the competing risk method.

† $P < .01$.

‡ $P < .05$.

Statistical Analyses

Univariate overall survival (OS) and AML transformation (AML-T) analysis was performed by using the Kaplan-Meier method.¹⁵ The starting point for follow-up was the time of the first cytogenetic examination, which marks the time of the first contact with an academic center and inclusion in the database (Figure A1, online only). Transformation to AML was assessed as defined by the FAB classification (blast count < 30%). Differences in time-to-event analyses were calculated by means of the log-rank test.¹⁶ AML-T was calculated by using the competing risk method, and the Gray test was applied to compare differences in AML-T.^{17,18} Multivariate analysis was performed by using a Cox regression hazard model defining OS and AML-T as end points. A normal karyotype, cytogenetic good risk as defined by the IPSS, and a blast count < 5% were considered reference categories by assigning them a hazard ratio (HR) of 1.0. *P* values < .05 were defined as significant and those < .01 as

highly significant. To allow for analysis of biologic variables not influenced by therapy, time-to-event analyses were performed for patients treated with supportive care exclusively. Subsequently, the treatment subgroups as defined above were analyzed separately to study the same prognostic factors under the influence of the respective therapies.

RESULTS

General Findings

In all, 2,351 patients were included, 988 (41.7%) originating from the GA database and 1,363 (57.9%) from the MDA database. The median age of patients was 66 years (range, 17 to 94 years), and the

Fig 1. (A-D) Cumulative survival and cumulative risk of acute myeloid leukemia (AML) transformation in International Prognostic Scoring System (IPSS) cytogenetic and French-American-British classification criteria bone marrow blast count subgroups (univariate analysis; patients treated with supportive care exclusively).

ratio of males to females was 1.7:1, which is in agreement with other studies of large MDS patient cohorts.^{5-7,11} Supportive care only was given to 1,292 patients (55.0%), 813 patients (34.6%) received AML-type therapy, and the remaining 236 patients (10.0%) received other therapies as described above. A normal karyotype was observed in 49.2% of all patients ($n = 1,156$), and 458 karyotypes (19.5%) were classified as complex ($\geq$ three abnormalities). The distribution of cytogenetic subgroups was comparable to the observations in other studies^{6,7,11}: 39.4% of patients ($n = 896$) had $< 5\%$ blasts, 23.3% ($n = 531$) had 5% to 10% blasts, 23.0% ($n = 523$) had 11% to 20% blasts, and 14.3% ($n = 325$) had 21% to 30% blasts (Table 1).

Univariate Analysis of OS and AML-T

After performing Kaplan-Meier analyses on patients treated with supportive care exclusively, the influence of cytogenetics on survival was in agreement with the findings reported for the International MDS Risk Analysis Workshop (IMRAW) database.⁶ Specifically, a normal karyotype ($n = 654$), $\text{del}(5q)$ ($n = 97$), $\text{del}(20q)$ ($n = 34$), or the loss of a Y chromosome ($n = 32$) within a noncomplex karyotype, for a total of 817 patients—was defined as the IPSS good-risk cytogenetic group; this group was associated with a good prognosis concerning OS and AML-free survival (median OS, 36.6 months; 1-year cumulative AML risk, 5.2%). A total or partial monosomy 7 (non-complex; $n = 46$) as well as complex abnormalities ($n = 191$) in combination defined the IPSS poor-risk cytogenetic group ($n = 237$). This group was identified as having unfavorable prognostic factors (median OS, 7.5 months; 1-year cumulative AML risk, 13.0%).

Categorizing these karyotypes into the cytogenetic IPSS classification system also led to a clear separation ($P < .01$ for OS) of prognostic subgroups regarding OS as well as cumulative risk of AML (Table 2 and Figs 1A and 1B). Similarly, the bone marrow blast count, described as an independent prognostic factor in MDS, showed a strong correlation with OS and AML-T. A blast count $< 5\%$ was associated with a good prognosis (median OS, 44.8 months) and a low risk of AML-T (1-year cumulative risk, 3.5%). In contrast, in patients with $> 20\%$ blasts, median OS was only 8.3 months ($P < .01$). Interestingly, patients with 5% to 10% blast count (median OS, 14.4 months) versus 11% to 20% blast count (median OS, 15.8 months) did not differ significantly from each other (Fig 1C). Similar observations were made regarding AML-free survival according to the number of bone marrow blasts (Fig 1D). When comparing the respective subgroups, we found that an increased blast count ($> 20\%$) constituted a comparable prognostic factor regarding AML-T (1-year risk, 20.5% compared with 13.0% in poor-risk cytogenetic findings). Surprisingly, complex abnormalities not involving chromosomes 5 and/or 7 were associated with an intermediate risk of AML-T in the subgroup of patients treated with supportive care (1-year risk, 6.5%). When comparing patients in the supportive care group who had complex abnormalities with patients harboring the same complex rearrangements but were treated with intensive chemotherapy, we observed significantly lower numbers of bone marrow blasts in the supportive care group (blast count $< 5\%$, 25.6% of patients ν 10.9%, respectively, $P < .01$; median blast count, 8% ν 15%, respectively, $P < .01$). This finding highlights the existence of a clinically discernable subgroup of patients with the combination of complex abnormalities and low blast counts that did not receive disease-altering therapy. Our data indicate that in this subgroup, complex karyotypic

changes are associated with an increased risk concerning OS but not AML-T.

Multivariate Analyses

The following were considered for inclusion in the multivariate model: site (German-Austrian ν MDA), age, sex, IPSS cytogenetic

Fig 2. Discriminatory power of International Prognostic Scoring System (IPSS) cytogenetic subgroups in distinct therapy categories. (A) Best supportive care; (B) chemotherapy; (C) other therapy.

subgroup [good *v* intermediate *v* poor], and bone marrow blast count [$< 5\%$ *v* 5% to 10% *v* 11% to 20% *v* $> 20\%$] as covariables (Table A1, online only). We first analyzed the 1,185 of 1,292 patients treated with supportive care for whom complete data were available; in 1,069 of these 1,185 patients, data regarding AML-T were also available. Figures 2A to 2C and Table 2 give an overview of the Cox regression model results. In agreement with the results of univariate analysis (Table 2), complex abnormalities were strongly associated with a poor prognosis for OS, while the prognostic impact of a total or partial monosomy 7, when occurring in a noncomplex setting, was more intermediate (HR, 1.9; $P < .01$). Complex abnormalities including aberrations of the chromosomes 5 and/or 7 defined the upper extremity of risk groups with an HR of 4.8 ($P < .01$). The prognostic impact related to the bone marrow blast count groups also confirmed the results of the univariate calculations showing an increasing risk when exceeding the blast count of 5%, although the 5% to 10% group (HR, 2.1; $P < .01$) and the 11% to 20% group (HR, 2.0; $P < .01$) did not differ significantly from each other. By passing the 20% threshold, the HR escalated to 3.1 ($P < .01$). Concerning AML-free survival, similar relations were observed with the exception of monosomy 7 which, in this context, was associated with a high risk of AML-T (HR, 3.6; $P < .01$). Complex abnormalities without involvement of chromosomes 5 and/or 7 were correlated with a lower risk of AML-T (HR, 0.7; P not significant) compared with complex cases harboring chromosome 5 and/or 7 abnormalities (HR, 1.4; $P < .01$). In OS analysis, the risk of poor-prognosis karyotypes (HR, 3.3; $P < .01$) was similar to the risk of increased ($> 20\%$) blast counts (HR, 3.1; $P < .01$) or, in complex cases including chromosome 5 and/or 7, clearly exceeded it (HR, 4.8; $P < .01$). Regarding AML-T, a blast count $> 20\%$ was a higher risk (HR, 2.9; $P < .01$) compared with an IPSS poor-risk karyotype (HR, 1.7; $P < .05$).

Influence of Cytogenetics and Bone Marrow Blast Count in Therapy Subgroups

To test whether the results shown above were also applicable in patients receiving treatment other than best supportive care, univariate and multivariate analyses were also performed. Interestingly, the

cytogenetic subgroups as defined by the IPSS maintained their predictive power concerning OS independent of the therapy applied. The prognostic impact of good-, intermediate-, and poor-risk cytogenetics differed highly significantly ($P < .01$) between the subgroups for OS (Table 3 and Table 4; Figs 2A to 2C), even if the median OS in each group differed depending on the therapy applied. Similar results were observed for AML-T, although the results did not reach statistical significance in each group. Multivariate analysis showed no significant differences concerning OS between the good- and intermediate-risk IPSS cytogenetic subgroup in patients treated with chemotherapy or other therapy, although the good- and poor-risk IPSS subgroups differed highly significantly ($P < .01$) in each therapy subgroup. The univariate and multivariate analyses revealed that, independent of the therapy applied, the prognostic impact of poor-risk cytogenetics on OS is as unfavorable as the highest blast counts (21% to 30%). Applying this perception to the original IPSS and assigning poor-risk cytogenetic findings 2.0 points (compared with 1.0 points in the original IPSS) leads to a change of 26 patients (5.3% of the intermediate-1 patients) from the IPSS intermediate-1 to the intermediate-2 group and 182 patients (38.8% of the intermediate-2 patients) from the intermediate-2 to the high-risk group, finally inducing a risk group change in 16% of all patients.

DISCUSSION

In this study, we analyzed the prognostic impact of cytogenetics and bone marrow blast counts in a large, well-characterized MDS patient cohort, validating the prognostic impact of previously published predictive factors for OS and risk of AML-T by univariate analysis. In a second step, we focused on the prognostic weighting of cytogenetics and blast counts with implications for existing and future predictive scoring systems and found by multivariate analysis that poor-risk cytogenetics and high blast counts remain strong independent prognostic factors irrespective of therapy. Recently, several shortcomings of the IPSS have been discussed,^{8,19,20-23} but it remains the most commonly used prognostic system. On the basis of a tentative

Table 3. Overall Survival and AML Transformation in Univariate Analysis of Therapy Subgroups

Category	Overall Survival						AML Transformation (cumulative risk)*					
	Best Supportive Care		AML-Like Chemotherapy		Other Therapy		Best Supportive Care		AML-Like Chemotherapy		Other Therapy	
	Median	No.	Median	No.	Median	No.	% 1-year/ 5-year	No.	% 1-year/ 5-year	No.	% 1-year/ 5-year	No.
IPSS cytogenetic subgroup	†		†		†		<i>P</i> N/S		†		<i>P</i> N/S	
Good	36.6	817	23.1	409	26.5	142	5.2/11.4	770	24.2/35.2	391	11.5/18.1	142
Intermediate	25.7	203	20.2	149	19.4	36	6.9/15.1	177	35.4/57.2	139	16.7/19.4	36
Poor	7.5	237	7.8	250	11.5	56	13.0/16.8	214	32.1/38.9	238	15.7/22.9	58
Bone marrow blast count (%)	†		†		†		†		†		†	
< 5	44.8	648	27.0	131	25.3	97	3.5/9.0	610	23.6/43.2	124	5.2/7.2	97
5-10	14.4	285	15.9	173	17.5	65	8.4/16.4	269	18.9/30.5	171	7.8/21.0	65
11-20	15.8	197	13.0	262	16.4	56	10.3/16.5	179	27.3/36.5	257	26.0/27.9	56
21-30	8.3	102	13.4	205	9.7	14	20.5/23.3	87	40.6/44.8	195	42.9/50.0	14

Abbreviations: AML, acute myeloid leukemia; IPSS, International Prognostic Scoring System; N/S, not significant.

*Calculated by the competing risk method.

† $P < .01$.

‡ $P < .05$.

Table 4. Overall Survival and AML Transformation in Multivariate Analysis of Therapy Subgroups

Category	Overall Survival						AML Transformation*					
	Best Supportive Care (n = 1,185)		AML-Like Chemotherapy (n = 771)		Other Therapy (n = 231)		Best Supportive Care (n = 1,069)		AML-Like Chemotherapy (n = 746)		Other Therapy (n = 230)	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
IPSS cytogenetic subgroup												
Good	1.0	Ref.	1.0	Ref.	1.0	Ref.	1.0	Ref.	1.0	Ref.	1.0	Ref.
Intermediate	1.3	1.1 to 1.7†	1.2	0.9 to 1.5	1.4	0.9 to 2.2	1.2	0.8 to 2.0	1.6	1.2 to 2.1†	1.1	0.4 to 2.0
Poor	3.3	2.8 to 4.0†	2.7	2.2 to 3.2†	2.3	1.6 to 3.3†	1.7	1.1 to 2.6‡	1.5	1.1 to 1.9†	1.0	0.5 to 2.0
Bone marrow blast count (%)												
< 5	1.0	Ref.	1.0	Ref.	1.0	Ref.	1.0	Ref.	1.0	Ref.	1.0	Ref.
5-10	2.1	1.7 to 2.5†	1.3	1.0 to 1.7	1.1	0.7 to 1.5†	2.1	1.4 to 3.3†	1.0	0.6 to 1.4	3.0	1.2 to 7.6‡
11-20	1.9	1.6 to 2.4†	1.5	1.1 to 1.9†	1.2	0.8 to 1.7†	2.2	1.4 to 3.6‡	1.4	1.0 to 2.0‡	5.3	2.1 to 13.1†
21-30	3.0	2.3 to 3.9†	1.4	1.1 to 1.8‡	1.8	1.0 to 3.4†	2.9	1.7 to 5.1†	1.7	1.2 to 2.4†	12.9	4.2 to 39.4†

Abbreviations: AML, acute myeloid leukemia; HR, hazard ratio; IPSS, International Prognostic Scoring System; Ref., reference category.

*Calculated by the competing risk method.

† $P < .01$.‡ $P < .05$.

univariate analysis in a smaller data set, correction of an imbalance of prognostic weighting has been previously suggested.⁹ The WHO Classification-Based Prognostic Scoring System (WPSS) published in 2007⁸ also assigned a higher weight to poor-risk cytogenetics. Our present data clearly indicate that within the IPSS, poor-risk cytogenetics, rated with 1.0 points, are underestimated compared with blast counts, which are rated with 2.0 points in the most unfavorable group (21% to 30%). Therefore, we anticipate that survival prediction for individual patients and overall predictive accuracy of a revised international scoring system would be improved by a stronger weighting of adverse cytogenetic factors.

On the basis of our data, cytogenetic abnormalities were associated with the same risk as that described in other, large-scale studies.^{5-7,11} The prognostic impact of poor-risk cytogenetics in our study was as unfavorable and, in case of complex abnormalities involving chromosomes 5 and/or 7, clearly more unfavorable as the prognostic impact of an elevated (21% to 30%) blast count. This finding was observed especially for OS, although in AML-free survival, the blast count was the strongest prognostic predictor in univariate and multivariate analysis. In the latter case, the relative risk concerning OS was comparable between poor-risk cytogenetics and an increased bone marrow blast count (HR, 3.3 for poor-risk cytogenetics v 3.1 for a blast count of 21% to 30%). Furthermore, focusing on distinct cytogenetic subgroups, it becomes evident that complex abnormalities including chromosomes 5 and/or 7 are associated with a markedly increased risk of shortened OS and AML-T. This finding gains further importance since the majority of the patients with complex abnormalities harbor chromosome 5 and/or 7 abnormalities. Results published previously by our group¹¹ have shown that there is a strong correlation between the number of abnormalities per patient and prognosis, which reflects the genomic instability of the respective clone. By classifying patients with complex abnormalities according to the number of abnormalities, patients with three abnormalities show a clearly better prognosis than those with more than three abnormalities.^{11,24} However, because complex abnormalities involving chromosomes 5 and/or 7 are associated with a higher number of abnormalities (unpublished data), it remains unclear whether the overall genomic instability or a specific

pathobiology linked to chromosome 5 and/or 7 anomalies accounts for this unfavorable clinical behavior.

Although we were primarily interested in the weighting of prognostic parameters in patients treated with best supportive care exclusively, data analysis also allowed for comparison of patients treated with different types of therapy. Interestingly, poor-risk cytogenetics retained their discriminatory power within the IPSS independent of the bone marrow blast count, and the applicability of the IPSS cytogenetic classification could be demonstrated in all therapeutic subgroups.

In summary, we demonstrated the independent influence of poor-risk cytogenetics on OS, which was as unfavorable as increased blast counts (21% to 30%) in this retrospective study. Because the upcoming revision of the IPSS will be based on the WHO classification of MDS, which marks the threshold between MDS and AML at 20% bone marrow blasts, 11% to 20% blasts will constitute the most unfavorable group. Consequently, poor-risk cytogenetic findings in this more narrowly defined group of MDS will gain additional weight as unfavorable prognostic markers in relation to blast counts.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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