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The myelodysplastic syndromes: predictive value of eight prognostic systems in 143 cases from a single institution

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ABSTRACT

Background and Objective. Despite the fact that several prognostic systems for myelodysplastic syndromes (MDS) have been proposed, few studies have been designed to test their effectiveness in independent patient populations. The aim of this study was to compare the prognostic value of 8 previously described prognostic systems in a series of consecutive MDS patients observed at a single institution over a 10-year period.

Design and Methods. One hundred and forty-three patients were diagnosed as having myelodysplastic syndrome (MDS) according to the French-American-British (FAB) criteria. They were studied retrospectively in order to assess the prognostic value of the FAB classification and 7 other prognostic systems.

Results. On the basis of data at diagnosis, all investigated systems effectively stratified patients into groups with different life expectancies and identified a subset of patients with poor clinical outcome. However, the systems had different outcomes concerning median survival of patients classified as low-risk, ranging from less than 3 years for the Mufti scoring system to more than 8 years for the FAB classification modified according to Rosati *et al*. Moreover, patient distribution into different risk categories was quite different with the different prognostic systems.

Interpretation and Conclusions. When applied to our case series, some of the prognostic systems had a much lower prognostic value than in the patient population from which they derived. This evidence suggests that testing of prognostic systems in independent case series is necessary before using the systems in clinical practice.

Key words: myelodysplastic syndromes, prognostic systems, survival, FAB classification

The myelodysplastic syndromes (MDS) are a heterogeneous group of disorders involving the stem cell and affecting predominantly elderly patients. They are likely to become more prevalent with the increase in an ageing population and the increasingly widespread and successful use of chemotherapy and radiotherapy.[1] The clinical course of patients with MDS is very varied, ranging from an isolated anemia for more than 10 years to an illness rapidly evolving into acute leukemia fatal within weeks. The great variability in the natural history of MDS complicates decision-making regarding therapy. Intensive chemotherapy and bone marrow transplantation currently offer the only potentially curative treatment, but these procedures should be considered only for patients with a short life expectancy, since a large number of MDS transplanted patients are destined to die of toxic effects of therapy.[2,3] At the opposite end of the therapeutic spectrum, supportive therapy is probably the best option for older patients with less aggressive forms of MDS. Therefore, prognostic characterization of individual MDS patients is an essential prerequisite for a proper risk-based therapeutic choice, but unfortunately this characterization remains a matter of debate. The French-American-British (FAB) classification[4] has a good predictive value, but it is not fully satisfactory: patients with refractory anemia with excess of blasts (RAEB), RAEB in transformation (RAEB-t) and chronic myelomonocytic leukemia (CMML) have a uniformly poor prognosis, but survival is very varied within patients with refractory anemia (RA) and RA with ring sideroblasts (RARS). To overcome this problem, Rosati *et al*.[5] proposed adding a fifth subset to the FAB classification, named *refractory cytopenia with multilineage dysplasia* (RCMD) and characterized by multilineage proliferation and dysplasia, but no increase in the number of peripheral blood or bone marrow blasts, and no Auer rods or monocytosis; in the authors experience these features identify a group of patients with an unfavorable clinical outcome.

To improve prognostic characterization of MDS, over the past decade many scoring systems taking into account different clinical and laboratory parameters have also been developed. Obviously, they were quite effective in the patient series used to drive them, but this fact is not sufficient to validate them, and their utility awaits further testing in populations other than that from which they were derived. To bring a contribution to this issue, we applied six prognostic scoring systems,[6-11] the FAB classification, and the FAB classification modified according to Rosati

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et al.[5] to MDS patients followed in our institution over the last 10 years, and directly compared their prognostic value.

Design and Methods

Patients

The records of patients observed in our institution between 1986 and 1996 were examined, and 143 cases of primary MDS were found who had not received intensive chemotherapy (11 patients affected by RAEB or RAEB-t, observed after 1994, were excluded because of aggressive polychemotherapy) and for whom adequate clinical information was available [97 patients were observed until death (median follow-up: 14 months), 14 were lost to follow-up (median follow-up: 12 months), and 32 were still alive at the end of 1996 (median follow-up: 55 months)]. To confirm the diagnosis of MDS, all the initial bone marrow and peripheral blood smears were reviewed. On the basis of the FAB classification, 52 patients had RA, 14 RARS, 37 RAEB, 32 RAEB-t and 8 CMML. The clinical and hematologic findings of the FAB subgroups are reported in Table 1.

Patients were also classified according to the FABm classification. On the basis of bone marrow and peripheral blood findings, 32 patients (25 previously classified as RA and 7 as RARS) fulfilled the criteria proposed for RCMD, in that they had less than 5% bone marrow blasts, trilineage dysplasia, no Auer rods and too few monocytes for a diagnosis of CMML.

Prognostic scoring systems proposed by Mufti *et al.*[6] (calculated with neutrophil and platelet counts, hemoglobin level and bone marrow blast percentage), Sanz *et al.*[7] (age, platelet count and bone marrow blasts), Goasguen *et al*.[8] (platelet count, hemoglobin level and bone marrow blasts) and Morra *et al.*[9] (age, platelet count, hemoglobin level and bone marrow blasts) were applied to all patients based on data obtained at the time of each patient's diagnosis; a scoring calculation according to the International Prognostic Scoring System-IPSS[11] (bone marrow blasts, number of cytopenias and karyotype) and Morel *et al.*[10] (platelet count, bone marrow blasts and karyotype) was possible in only 98 subjects (Table 1), because karyotype at diagnosis was not available for 45 subjects (cytogenetic investigation not performed at diagnosis in 30 cases, lack of evaluable mitosis in 15 cases).

Statistical analysis

Statistical analysis was performed with the Statistica 5.1 package (StatSoft, Tulsa, OK, USA). Patient survival was analyzed by the Kaplan-Meier method[12] from the date of diagnosis until death due to any cause (97 cases) or until the last patient contact (15 patients lost to follow-up and 31 alive up to December 1996). Survival curves were compared with the log-rank test.[13] Cox's proportional-hazards model was used to analyze the association between risk categorization and the cause of death (Cox, 1972).[14]

Results

Table 2 shows the patients' distribution into subgroups identified by FAB, FABm and by the scoring systems. This table, together with Tables 3 and 4, refers to the 98 patients with cytogenetic characterization at diagnosis, but similar results were obtained when the grouping systems not requiring chromosomal mapping were applied to all 143 cases (data not shown). It is evident from this table that patient distribution into low, intermediate and high risk categories was quite different with the different grouping systems: in particular, a large number of patients were allocated to the low risk group by the FAB classification, while only a few patients were categorized as low risk by the Goasguen and IPSS scoring systems.

Survival percentiles of patients with different risk categorizations are reported in Table 3, together with the statistical significance of survival differences observed among different risk categories within each prognostic system. All the systems were able to stratify patients into at least three groups with different life expectancies (IPSS, FAB and FABm identified 4 groups) and to identify a group of subjects with very poor clinical outcome. However, they gave different results in the identification of long survivors: only the

Table 1. Clinical and hematologic findings in patients classified according to FAB.

Group	*No. of patients*	*Age (years)*	*Hemoglobin (g/dL)*	*Platelets (x10⁹/L)*	*Leukocytes (x10⁹/L)*	*Neutrophils (x10⁹/L)*
RA	52 (33*)	64.5 (31-86)	9.7 (4.8-86)	161 (27-307)	4.2 (1.1-14.7)	2.33 (0.23-11.3)
RARS	14 (10)	65.8 (42-84)	8.3 (5.6-11.2)	267 (85-551)	5.5 (1.5-9.0)	2.7 (0.75-5.1)
RAEB	37 (32)	61.2 (21-80	8.9 (5.6-14.9)	136 (8-562)	6.4 (1.2-13.6)	2.7 (0.08-11.4)
RAEB-t	32 (18)	60.6 (22-77)	8.9 (4.7-13.8)	67 (7-211)	4.4 (0.6-14.7)	2.21 (0.03-14.7)
CMML	8 (5)	63.3 (39-88)	9.5 (6.1-12.5)	112 (22-201)	14.6 (3.7-48.2)	8.1 (0.99-33.2)

** No. of patients for whom cytogenetic analyses were available.*

Table 2. Patient distribution (%) in FAB,[4] FABm[5] and prognostic subgroups identified according to the scoring systems of Mufti et al.,[6] Sanz et al.,[7] Goasguen et al.,[8] Morra et al.,[9] Morel et al.,[10] and Greenberg et al.[11]

	Patient distribution (%)		
Risk category	LR	IR (IR1-IR2)	HR
Prognostic system			
Mufti	26	62	12
Sanz	37	38	25
Goasguen	11	36 33	20
Morra	24	32 32	12
Morel	34	38	28
IPSS	12	46 20	22
FAB	46	26 22	6
FABm	24	22 26	28

For the FAB classification: low risk (LR) = RA + RARS; intermediate risk 1 (IR1) = RAEB; intermediate risk 2 (IR2) = RAEBt; high risk (HR) = CMML; for the FABm classification: LR = RA + RARS; IR1 = RCDM; IR2 = RAEB; HR = RAEBt + CMML.

low risk group of FABm had a median survival time longer than 100 months, while *good prognosis* subjects identified by Mufti and Morra scoring systems had a life expectancy shorter than 40 months.

With the exception of Mufti's, Goasguen's and Morra's scoring systems, the investigated prognostic systems were also effective in predicting the cause of death, in that the great majority of patients classified as being at high and intermediate risk died of leukemic transformation, acute hemorrhage or infection, while the larger part of patients in the low risk group died of causes not directly related to MDS. The IPSS, Morel's scoring system and the FABm classification were particularly effective in this respect (Table 4).

Table 4. Cause of death of patients divided according to different grouping systems. Death was classified as directly related to MDS when it occurred because of acute leukemia, bleeding or infection and as not directly related to MDS in other cases. The percentage of patients in each category who died of a cause directly related to MDS is reported. For risk category definition see Table 2. The statistical significance (p) of the association between risk categorization and the cause of death is reported.

	Deaths related to MDS (%)			p value
Risk category	LR	IR (IR1-IR2)	HR	
Prognostic system				
Mufti	56	73	92	0.009
Sanz	48	75	83	0.001
Goasguen	80	50 79	83	0.005
Morra	71	58 72	92	0.07
Morel	36	83	86	0.0009
IPSS	0	58 100	92	0.00002
FAB	36	83 92	50	0.00002
FABm	30	50 83	92	0.0001

Discussion

Prognosis in MDS is extremely varied, with some patients remaining symptom-free for many years and living a long time and others dying from infection or hemorrhage within a few weeks or months of diagnosis. In our group of 143 patients, median survival from diagnosis was 18 months, but 20% of patients survived more than 100 months. Similar figures were obtained by Sanz and Sanz[15] from a meta-analysis of 1914 patients. Prognostic characterization of single patients at diagnosis could, therefore, be very useful to identify the best therapeutic strategy.

Although several biological parameters have been shown to have prognostic value in MDS, multivariate

Table 3. Survival time (months) of MDS patients related to their classification by different prognostic systems. The significance of differences in survival among the prognostic groups within each prognostic system is reported in brackets (log-rank P value). For abbreviations and further details see Table 2.

	Survival percentiles									Log-rank p-value
	25th			50th			75th			
Risk category	LR	IR (IR1-IR2)	HR	LR	IR (IR1-IR2)	HR	LR	IR (IR1-IR2)	HR	
Prognostic system										
Mufti	16.8	9.9	8.5	32.7	17.6	11.9	82.0	47.1	16.9	0.06
Sanz	21.7	8.1	10.9	64.3	14.4	11.9	117.0	31.7	24.4	0.007
Goasguen	25.1	12.1 7.0	10.9	50.1	32.7 11.9	15.1	92.9	65.5 29.1	22.4	0.009
Morra	17.1	7.0 11.6	7.2	39.6	12.3 15.7	11.9	93.7	40.1 29.9	26.2	0.07
Morel	19.1	9.9	9.9	62.3	16.8	12.4	117.2	36.1	19.6	0.01
IPSS	20.9	13.2 9.0	7.0	40.6	25.8 14.9	10.4	88.2	80.7 28.0	13.5	0.01
FAB	15.3	11.9 7.4	6.4	52.1	17.3 10.9	10.5	115.9	28.7 17.1	16.4	0.04
FABm	16.0	7.0 11.9	6.4	101.6	33.6 17.1	10.5	NR	83.2 28.7	16.4	0.01

NR = Not reached.

analyses have generally demonstrated that the importance of cytopenias and the percentage of bone marrow blasts, in addition to age, gender and karyotype, constitute the only independent determinants of survival.[11] In order to improve prognostic characterization, these parameters have been combined in several scoring systems.[16] All of them showed a good prognostic value in the case series which generated them, but few of them have been validated in independent patient series. For this reason, we applied six previously published scoring systems[6-11] to patients with primitive MDS observed in our institution over the last 10 years and compared their prognostic value with that of the FAB classification and Rosati's modification of it.[5] In our series, all prognostic systems were able to recognize groups of patients with different life expectancies on the basis of data at diagnosis. Moreover, median survival time of patients assigned to the high risk group was similar with all prognostic systems, ranging from 10.4 to 15 months. In contrast, grouping systems differed from one another in the number of risk categories they identified, the percent of subjects assigned to each risk category and the survival time of the low risk patients. IPSS, FAB and FABm recognized 4 groups of patients with different life expectancies, while only three were identified by the other prognostic systems. Concerning patient distribution, more than 30% of subjects were assigned to the low risk category by Sanz's and Morel's scoring system and by the FAB classification, 20-30% by the Mufti and Morra systems and by FABm, and less than 20% by the Goasguen system and by IPSS. Unexpectedly, survival time of low risk categories identified by different prognostic systems was not inversely related to their numerosity. For example, median survival of patients allocated to the low risk group was longer for the FAB and scoring systems of Sanz and Morel (containing 34-46% of patients) than for the IPSS and Goasguen's system (comprising 11-12% of patients). Moreover, low risk patients identified by FABm had by far the longest survival time, although the group was not the smallest.

What conclusions can be drawn from our data? Which was the best prognostic system in our series of patients? In our opinion, more than one answer is possible. First of all, we have to clarify what we expect of a prognostic system. If we need a prognostic system for the design and analysis of therapeutic trials, FAB, FABm, IPSS and the scoring systems of Sanz and Morel are all suitable, in that they allowed categorization of patients into 3-4 subsets with significantly different life expectancies. If we need to predict the clinical course of patients to select those who would benefit most from more aggressive therapy, as opposed to only supportive care, the most effective prognostic system was FABm, in that it was able to identify a 25% group of patients with a median survival longer than 100 months, while the other 75% had a median life expectancy shorter than 34 months. The FAB classification and Sanz's and Morel's systems allocated a higher proportion of patients to the low-risk category than FABm, but their median survival was shorter. The results obtained by the newest of the scoring systems, the IPSS, were disappointing in this respect. The IPSS assigned only 12% of patients to the low-risk group, but notwithstanding this, their median survival was no longer than 40.6 months, and 88 months after diagnosis only 25% of patients were still alive. We are unable to explain why the IPSS failed to identify very long survivors in our patients; however, our experience suggests that further testing in independent case series is required before the IPSS is routinely applied to risk-based decision-making in MDS.

Although FABm was able to identify two homogeneous subsets of patients, one with very long (RA and RARS) and one with short (RAEB, RAEB-t, CMML) survival, prognosis of the RCMD subgroup was less well defined, in that median survival was short (33.6 months), but 25% of patients were still alive 83 months after diagnosis. Therefore the FABm classification failed to define the prognosis of 22% of our patients clearly and its prognostic value cannot be considered fully satisfactory. Another drawback of the FABm classification is that identification of RCMD relies on morphological evaluation of bone marrow and peripheral blood dysplasia which, besides being time-consuming, is largely subjective and difficult to standardize.

In conclusion, our investigation indicates that none of the prognostic systems we applied to our MDS series was able to predict life expectancy of all individual patients, although the FABm classification was effective in the majority of them. Furthermore, our experience underlines the importance of testing prognostic systems in case series other than those from which they were derived, before using them in clinical situations.

Contributions and Acknowledgments

CLB was primarly responsible for the conception of this study and the writing of the paper. RG was responsible for review clinical records and statistical analysis. AP and EC contributed to the review of records. RI was responsible for reviewing slides. EA supervised the whole study. The order in which the names appear is based on the time spent in this research.

Disclosures

Conflict of interest: none.

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