Identification of novel cytogenetic markers with prognostic significance in a series of 968 patients with primary myelodysplastic syndromes

Francesc Solé
Elisa Luño
Carmen Sanzo
Blanca Espinet
Guillermo F. Sanz
José Cervera
María José Calasanz
Juan Cruz Cigudosa
Fuensanta Millà
Josep Maria Ribera
Encarna Bureo
Maria Luisa Martín
Eva Arranz
Lourdes Florensa

Background and Objectives. The main prognostic factors in myelodysplastic syndromes (MDS) are chromosomal abnormalities, the proportion of blasts in bone marrow and number and degree of cytopenias. A consensus-defined International Prognostic Scoring System (IPSS) for predicting outcome and planning therapy in MDS has been developed, but its prognostic value in a large and independent series remains unproven. Furthermore, the intermediate-risk cytogenetic subgroup defined by the IPSS includes a miscellaneous number of different single abnormalities of uncertain prognostic significance at present. The main aim of the present study was to identify chromosomal abnormalities with a previously unrecognized good or poor prognosis in order to find new cytogenetic markers with predictive value.

Design and Methods. We report the cytogenetic findings in a series of 968 patients with primary MDS from the Spanish Cytogenetics Working Group, *Grupo Cooperativo Español de Citogenética Hematológica (GCECGH)*.

Results. In this series of 968 MDS patients, we found various cytogenetic aberrations with a new prognostic impact. Complex karyotype, -7/7q- and i(17q) had a poor prognosis; normal karyotype, loss of Y chromosome, deletion 11q, deletion 12p and deletion 20q as single alterations had a good prognosis. Intermediate prognosis aberrations were rearrangements of 3q21q26, trisomy 8, trisomy 9, translocations of 11q and del(17p). Finally, a new group of single or double cytogenetic abnormalities, most of which are considered rare cytogenetic events and are usually included in the intermediate category of the IPSS, showed a trend to poor prognosis.

Interpretations and Conclusions. This study suggests that some specific chromosomal abnormalities could be segregated from the IPSS intermediate-risk cytogenetic prognostic subgroup and included in the low risk or in the poor risk groups.

Haematologica 2005; 90:1168-1178

Key words: myelodysplastic syndromes, karyotype, cytogenetics, prognosis, IPSS.

"Grupo Cooperativo Español de Citogenética Hematológica" (AEHH), Laboratori de Citogenètica i Biologia Molecular, Servei de Patologia, Hospital del Mar-IMAS (Barcelona), Hospital Universitario Central de Asturias (Oviedo) Hospital Germans Trias i Pujol (Badalona), Hospital la Fe (Valencia), Hospital Universitario (Pamplona), Centro Nacional de Investigaciones Oncológicas (Madrid), Servicio de Hematología, Hospital Universitario Marqués de Valdecilla, Santander, Servicio de Genética, Hospital Doce de Octubre, Madrid, Unidad de Genética, Servicio de Hematología, Hospital la Princesa, Madrid, Spain.

Correspondence:
Francesc Solé, Laboratori de Citogenètica i Biologia Molecular, Servei de Patologia, Hospital del Mar, Passeig Marítim 25-29, 08003 Barcelona, Spain.
E-mail: fsole@imas.imim.es

The myelodysplastic syndromes (MDS) constitute a heterogeneous group of hematologic disorders characterized by peripheral blood cytopenia(s) in the presence of hypercellular bone marrow with features of ineffective hematopoiesis. MDS are associated with a high risk of progression to acute leukemia and with an overall short survival, death being generally due to the consequences of cytopenias or progression to acute leukemia.[1] MDS are classified by the French-American-British (FAB) group, based on the percentage of bone marrow and peripheral blood blasts, the percentage of bone marrow ringed sideroblasts, and the level of circulating monocytes, into the following groups: refractory anemia (RA), refractory anemia with ringed sideroblasts (RARS), refractory anemia with excess of blasts (RAEB), refractory anemia with excess of blasts in transformation (RAEB-t) and chronic myelomonocytic leukemia (CMML). Recently, the Wordl Health Organization (WHO) classification proposed the following groups:[2] RA, RARS, refractory cytopenia with multilineage dysplasia, RAEB, MDS unclassifiable, and MDS associated with isolated del(5q) chromosome abnormality. Two categories are recognized within the RAEB group: RAEB-1 defined by 5-9% blasts in the bone marrow and <5% blasts in the blood, and RAEB-2, defined by 10-19% blasts in the bone marrow. The WHO classification is more stringent than the FAB classification regarding the percentage of blasts. For this reason, some MDS classified in the FAB classification are now considered as acute leukemia using the criteria of the WHO classification. MDS with an isolated del(5q) is the

only cytogenetic entity considered in the WHO classification. MDS are not associated with any specific chromosomal abnormality, but the following abnormalities are characteristic of these disorders: deletion 5q, monosomy 7, deletion 7q, trisomy 8, deletion 11q, deletion 12p, and deletion 20q.[3-16]

With respect to prognostic variables, several studies have demonstrated the prognostic power of the platelet count, the percentage of bone marrow blasts, and age of the patient.[17,18] Some studies that included large series of patients with MDS and cytogenetic results also demonstrated the prognostic influence of cytogenetics by multivariate analysis. In these studies, patients with a complex karyotype were generally found to have shorter survival and a higher incidence of evolution to acute myeloid leukemia (AML) compared to patients with a normal karyotype.[12,13] An international study group on MDS proposed a score, the International Prognostic Scoring System (IPSS), to stratify patients according to the percentage of blasts in bone marrow, the number of cytopenias and the karyotype.[19] Three categories of karyotype were proposed: those with a good prognosis including a normal karyotype, deletion 5q as a single anomaly, deletion 20q as a single anomaly and loss of Y chromosome; those with a poor prognosis including complex karyotypes (more than three abnormalities) or chromosome 7 anomalies; and those with an intermediate prognosis, comprising all other abnormalities. However, given the small number of series including large number of patients with MDS and karyotypic information,[19-21] the prognostic significance of less frequent cytogenetics abnormalities remains to be analyzed. In this report, we describe the cytogenetic findings in a series of 968 patients with MDS and, using univariate and multivariate analyses, we analyze the prognostic value of the cytogenetic aberrations, especially those belonging to the intermediate risk group.

Design and Methods

Patients

This retrospective study is based on 968 consecutive patients who were referred to hospitals affiliated to the Spanish Cytogenetic Working Group between January 1984 and May 2004. Only patients that fulfilled FAB criteria for MDS were included.[1] Patients with an ambiguous diagnosis of MDS, those who had previously received chemo/radiotherapy, and those with MDS secondary to a previous malignancy were excluded from the analysis. Table 1 provides a summary of the main clinical data of the patients. Among the 968 patients, 696 received only supportive care, 159 were treated with monotherapy, 77 with chemotherapy (25 with fludarabine, cytarabine, idarubicin and granulocyte colony-stimulating factor, and 52 with standard therapy for acute myeloid leukemia). Twenty-two of those patients who were intensively treated underwent stem cell transplantation.

Investigators from the participating institutions completed a standard registration form for each patient detailing the clinical, hematologic and cytogenetic features at presentation and the clinical outcome (survival time from diagnosis and time until evolution to acute myeloid leukemia).

Cytogenetic studies

The cytogenetic analysis of bone marrow samples was performed at the individual centers following standard procedures. The results were reviewed and collated centrally by the main investigators (FS, EL, and CS). Whenever possible, at least 20 metaphases were analyzed and four of them karyotyped. Chromosomes were identified and karyotypes described according to the International System for Chromosome Nomenclature (ISCN).[22] A karyotype was considered complex when more than two cytogenetic abnormalities were found. When two or more clones were noted in a patient with two aberrations, the patient was categorized in the complex aberration group, whereas patients with two karyotypically independent clones with a single change were categorized in the two-aberration groups. In patients with loss of Y chromosome constitutional karyotyping with phytohemagglutin was carried out in order to confirm that the aberration was not constitutional.

Cytogenetic data and some clinical information concerning 112 patients who were managed at Hospital Central l´Aliança (Barcelona), Hospital Vall d'Hebron (Barcelona) and Hospital Universitario La Fe (Valencia) have been previously reported elsewhere[11] as have the cytogenetic data from the first 640 patients.[20]

Analysis of prognostic factors for survival and progression to acute leukemia

The following parameters were analyzed to determine their possible association with survival or evolution to acute leukemia: age, sex, hemoglobin (Hb) concentration, platelet count, absolute neutrophil count (ANC), number of cytopenias, percentage of blasts in bone marrow, and karyotype. The FAB classification,[1] Spanish prognostic score (SPS)[18] and IPSS[19] were also evaluated. The influence of the WHO classification[2] was only evaluated in 288 patients for whom we have data on the dysplasia. Among these patients, 214 fulfilled the criteria of the WHO classification.

Table 1 . Chromosomal abnormalities according to FAB subtype.

Variable	No. of patients (%)	No.(%) RA	RARS	RAEB	RAEB-t	CMML	p value
Karyotype		264	160	269	105	170	
Normal	514 (53.0)	151 (57.0)	106 (66.0)	109 (41.0)	31 (30)	117 (69.0)	< 0.0001
Abnormal	454 (47.0)	113 (43.0)	54 (34.0)	160 (59.0)	74 (70)	53 (31.0)	
Complex	107 (11.1)	13 (12.1)	8 (7.5)	51 (47.7)	28 (26.2)	7 (6.5)	< 0.0001
Single or double	347 (35.9)	100 (28.8)	46 (13.3)	109 (31.4)	46 (13.3)	46 (13.3)	
Complex:							
5 or 7 involved	71 (66.4)	8 (11.3)	5 (7.0)	33 (46.5)	21 (29.6)	4 (5.6)	0.44
Hyperploid	6 (5.6)	1 (16.7)	1 (16.7)	4 (66.7)	7 (23.4)	3 (10.1)	
Others	30 (28.0)	4 (13.3)	2 (6.7)	14 (46.9)	–	–	
IPSS cytogenetic prognostic subgroups*							
good	556 (62)	185 (70)	124 (77)	134 (50)	37 (35)	76 (74)	< 0.0001
intermediate	199 (22)	59 (22)	27 (17)	63 (23)	31 (30)	19 (18)	
poor	146 (16)	20 (8)	9 (6)	72 (27)	37 (35)	8 (8)	
Single abnormalities							
r 3q21q26	6 (0.6)	2 (0.8)	1 (0.6)	1 (0.4)	1 (1)	1 (0.5)	0.96
del (5q)	55 (5.7)	23 (9)	5 (3)	22 (8)	4 (4)	1 (0.5)	0.005
-7/del (7q)	43 (4.4)	8 (3)	2 (1)	19 (7)	10 (9.5)	4 (2)	0.02
-7	29 (3)	6 (2)	1(0.6)	14 (5)	6 (6)	2 (1)	0.08
del(7q)	14 (1.4)	2 (0.8)	1(0.6)	5 (2)	4 (4)	2 (1)	0.37
+8	56 (5.8)	17 (6)	9 (5.6)	15 (5)	5 (5)	10 (6)	0.55
del or t(11q)	13 (1.3)	4 (1.5)	4 (2.5)	4 (1.5)	1 (1)	_	0.31
del 11q/t11q	7/6	2/2	3/1	2/2	–/1	–/–	0.53
del (12p)	13 (1.3)	3 (1)	2 (1)	7 (2.5)	_	1 (0.6)	0.36
i(17q)	10 (1)	1 (0.4)	_	5 (2)	3 (3)	1 (0.6)	0.19
del (17p)	5 (0.5)	2 (0.8)	1 (1)	_	_	2 (1)	0.17
del (20q)	13 (1.3)	4 (1.5)	5 (3)	2 (0.7)	1 (1)	1 (0.6)	0.11
+21	8 (0.8)	_	_	1 (0.4)	1 (1)	6 (3.5)	<0.0001
-Y	17 (1.8)	5 (2)	6 (4)	1 (0.4)	1 (1)	4 (2)	0.019
GCECGH cytogenetic subgroups*							
good	573 (63.6)	188 (71.2)	127 (79.4)	143 (53.2)	37 (35.2)	78 (75.7)	<0.0001
intermediate	70 (7.8)	23 (8.7)	13 (8.1)	19 (7.1)	7 (6.7)	8 (7.8)	
unknown	100 (11.1)	30 (11.4)	10 (6.3)	31 (11.5)	19 (18.1)	10 (9.7)	
poor	158 (17.5)	23 (8.7)	10 (6.3)	76 (28.3)	42 (40.0)	7 (6.8)	

*IPSS: International Prognostic Scoring System (Greenberg et al., 1997): good: normal, -Y, del (5q), del (20q); intermediate: +8, other single or double abnormalities; poor: complex (? 3 abnormalities) or chromosome 7 abnormalities. GCECGH (Grupo Cooperativo Español de Citogenética Hematológica) cytogenetic subgroups; good: normal, -Y, del(5q), del(11q), del (12p), del(20q); intermediate:+8, r3q21q26, t(11q), del(17p); poor: complex (?3 abnormalities),-7/del(7q), i(17q); unknown: other single or double abnormalities. *Excluding CMML patients with WBC counts > 12×10⁹/L.*

Statistical analysis

χ^2 tests were used to compare proportions. The Kaplan-Meier product limit method was used to estimate the actuarial probability of survival and the cumulative risk of leukemic transformation.[23] Survival was measured from diagnosis to death or last follow-up. All deaths, related or not to MDS, were considered as the endpoint of the follow-up interval. The time to transformation into acute leukemia was measured from diagnosis to development of acute leukemia. Data from patients dying from any cause before developing acute leukemia were censored at the date of death for the calculation of risk of leukemic transformation. Statistical comparisons between different actuarial curves were based on log rank tests[24] or, if applicable, the test for trend, as recommended by Peto *et al*.[25]

According to the prognostic significance of the cytogenetic abnormalities found as single anomalies, we proposed four categories of karyotypes, called *GCECGH* categories. These categories are as follows: *good prognosis*: normal karyotype, loss of Y chromosome, del(5q), del(12p), del(11q) and del(20q) as a single anomaly; *intermediate prognosis*: trisomy 8, rearrangements of 3q21q26, translocations of 11q, del(17p), trisomy 18 and trisomy 19; *poor prognosis*: complex karyotypes, monosomy 7, deletion 7q and i(17q); *unknown prognosis*: all remaining cases with single or double abnormalities.

Further multivariate analysis by the Cox proportional hazards regression method was used to identify the most significant independent prognostic factors related to survival and acute leukemic transformation. In a first phase the prognostic variables, with

the exception of IPSS and GCECGH cytogenetic subgroups, SPS[18] and IPSS,[19] were included in the multivariate regression procedure. In a second step, those characteristics entering the regression were included with the cytogenetic subgroups in a new multivariate regression to evaluate whether they added important prognostic information. In a third step the SPS and IPSS score were added to test whether they added important prognostic information to that already afforded by the scoring systems.

According to the weight (odds ratio) of the independent parameters, we proposed a new risk score for overall survival (OS), called the GCECGH score of OS and another risk score, for leukemic transformation (LT), called the GCECGH score for LT. Finally, after having introduced the newly defined risk values for OS and LT into the database, further univariate and multivariate analyses were performed in order to evaluate whether this new score stratified risk better.

For multivariate analyses, only cases with complete data were included (780 patients). Cases of CMML with >12×10^9 WBC/L were excluded from those multivariate analyses in which the IPSS, SPS and GCECGH score were required. Given the multiple comparison problems, the selected p value for considering differences as statistically significant in all analyses was ≥0.01. All tests were two-sided. All analyses were performed using the SPSS for Windows statistical data package.

Results

Clinical characteristics of the patients

The group included 553 males (57%) and 415 females (43%). The median age was 70 years (range 1 to 94). Two hundred and thirty-five patients (24.5%) were under 60 years of age. Of the 968 patients, 264 (27%) were classified as having RA, 160 (16%) as having RARS, 269 (28%) as having RAEB, 105 (11%) as having RAEB-t, and 170 (17%) as having CMML (Table 1). Sixty-seven patients (41.9%) with CMML presented the myeloproliferative variant. RAEB and RAEB-t subtypes correlated (p<0.001) with younger age (32.8% and 28.8%, respectively, were under 60 years old), number of cytopenias (two or three in 53.5% and 62.4% respectively) and high risk groups of scores. Of the patients with RAEB-t, all had an intermediate or high SPS score, 93% had an int-2 or high IPSS, 76.2% and 87.1% had a high or very high OS and LT GCECGH score, respectively. The data concerning hemoglobin concentration, platelet count, absolute neutrophil count, percentage of bone marrow blasts, cytopenias and the IPSS and SPS in the five different subtypes of MDS are shown in Table 1. At the time of analysis, 450 (46.5%) patients were still alive and 518 (53.5%) had died. The actuarial median survival of the 968 MDS patients was 2.5 years. Two hundred and eighteen patients progressed to acute leukemia, with a cumulative risk of leukemic transformation of 23% and 42% at 1 and 5 years, respectively.

Cytogenetic results

Of the 968 patients, 454 (47%) showed clonal karyotypic abnormalities at diagnosis. The frequency of the different chromosomal abnormalities and their relationship with the FAB classification are shown in Table 1. Cytogenetic abnormalities found as a single anomaly were gain of 1q, involvement of 3q, monosomy 5, del(5q), monosomy 7/del(7q), trisomy 8, trisomy 9, del or t(11q), trisomy 11, del(12p), rearrangement of 13q, i(17q), trisomy 17, trisomy 18, trisomy 19, del(20q), trisomy 21, monosomy 21 and loss of X and Y chromosomes. The most common abnormalities found were del(5q), monosomy 5, monosomy 7/del(7q), trisomy 8, rearrangement of 11q, del(12p), i(17q), del(20q) and loss of Y (Table 1). Complex karyotypes were observed in 107 patients, the incidence being 11.1% in the whole series of cases and 23.6% among those patients with abnormal karyotypes. Seventy-one (66.4%) of these complex karyotypes showed abnormalities involving chromosome 5 (deletion or monosomy), chromosome 7 (deletion or monosomy) or both.

Chromosomal abnormalities and FAB classification

As shown in Table 1, 113 patients with RA (43%), 54 with RARS (34%), 160 with RAEB (59%), 74 with RAEB-t (70%) and 53 with CMML (31%) showed a clonal abnormality. In RA the most frequent cytogenetic abnormalities were del(5q), trisomy 8, monosomy 7, loss of Y chromosome and del(20q); the most common abnormalities in RARS were trisomy 8, loss of Y chromosome, del(5q), and del(20q); the most common abnormalities in RAEB were del(5q), trisomy 8, monosomy 7, del(12p), and i(17q); in RAEB-t they were monosomy 7, trisomy 8, del(5q), del(7q), and i(17q), and in CMML the predominant abnormalities were trisomy 8, trisomy 21 and loss of Y chromosome.

Prognostic factors for survival and leukemic transformation

Univariate analysis

The results of the univariate analysis of prognostic factors for survival and risk of leukemic evolution are summarized in Table 2. Hemoglobin concentration, platelet count, number of cytopenias, proportion of bone marrow blasts, FAB subtype, IPSS and SPS scores showed a close association with short survival and high risk of leukemic transformation. Patients with an ANC < 1.5×10^9/L and elderly patients had an increased risk of acute leukemic transformation.

Table 2. Univariate analysis.

	Overall survival	*Leukemic transformation*
Variable	*p* value	*p* value
Gender	0.02*	0.27*
	0.11	0.55
	0.005	0.37
Age (year)	0.03*	0.01*
	0.16	0.02
	0.09	0.01
Hemoglobin (g/L)	< 0.0001	< 0.0001
Neutrophil count ($\times 10^9$/L)	0.04*	0.0003*
	0.11	0.0005
	0.07	0.0003
Platelet count ($\times 10^9$/L)	< 0.0001	< 0.0001
Bone marrow blasts (%)	< 0.0001	< 0.0001
Cytopenias	< 0.0001	< 0.0001
FAB subtype	< 0.0001	< 0.0001
IPSS score**	< 0.0001	< 0.0001
SPS score**	< 0.0001	< 0.0001
GCECGH cytogenetic subgroups**	< 0.0001	< 0.0001
GCECGH score**	< 0.0001	< 0.0001

*IPSS, International Prognostic Scoring System (Greenberg et al., 1997); SPS, Spanish Prognostic Score (Sanz et al., 1989). GCECGH (Grupo Cooperativo Español de Citogenética Hematológica). *Log-rank, Breslow and Tarone test; **Excluding CMML patients with WBC counts >12×10^9/L.*

Gender showed an association with survival (p=0.03) but not with evolution to acute leukemia.

Cytogenetic findings had a clear impact on overall survival and risk of leukemic transformation (Table 3). Patients with an abnormal karyotype had a shorter survival and higher risk of leukemic transformation than did those with a normal karyotype (p<0.0001). Patients with a single or two anomalies had increased survival and lower risk of evolution to acute leukemia than patients with complex karyotypes (p<0.0001). Within the group of complex karyotypes, the prognosis was similar for cases with or without involvement of chromosomes 5 and/or 7. The cytogenetic prognostic subgroups defined by the IPSS strongly influenced survival and risk of leukemic transformation. In our series, outcome regarding survival and evolution to acute leukemia for each specific abnormality was compared with the remaining set of abnormal cases with single aberrations: patients with del(5q), del(11q), del(12p), del(20q), and loss of Y chromosome had a longer survival than did the overall series of patients, whereas monosomy 7, del(7q), i(17q), rearrangement 1q, trisomy 9 and trisomy 11 showed a somewhat shorter survival, but these latter three abnormalities were infrequent. However, none of the chromosomal abnormalities found as single abnormalities, including those universally accepted as portraying good or poor prognosis, showed a statistically significant association with outcome when compared with the remaining cases, except for loss of Y chromosome (p=0.009), del(5q) (p=0.023), monosomy 7/del(7q) (p=0.0006), monosomy 7 (p=0.009), and del(17p) (p=0.04) for survival, and rearrangements of 3q (p=0.05), del(5q) (p=0.02) and monosomy 7 (p=0.03) for acute leukemia evolution. Only 5.9% of cases with loss of Y chromosome progressed to develop acute leukemia (p=0.03). We tried to ascertain whether any of the chromosomal abnormalities occurring as sole aberrations and without a previously recognized particular prognosis could be segregated from the miscellaneous intermediate-risk IPSS cytogenetic prognostic subgroup. For this propose, only abnormalities which occurred with an incidence >0.5% were evaluated.

The statistical analysis presented in all the tables was performed taking into account the new stratification of the patients according the cytogenetic findings of the GCECGH. The four GCECGH cytogenetic subgroups previously defined were helpful in separating the intermediate and unknown risk and showed a close association with survival and risk of leukemic transformation (Table 3, Figures 1 and 2).

The median survival for patients who received only supportive care (696/932) was 3.00 years and these patients were the longest survivors in our series (p=0.01). However, only 8.3% of patients were treated with intensive chemotherapy and, among them, 61% were less than 60 years old.

Prognostic score and survival according to the WHO classification

Table 4 summarizes the prognostic findings of 288 of our cases when they were reclassified using the WHO classification. The statistical analysis showed significant differences for survival and risk of leukemic evolution for all the categories.

Multivariate analyses for overall survival

By stepwise logistic regression, the cytogenetic subgroups of the IPSS and SPS scores showed a strong and independent relationship with survival, but the IPSS score did not show prognostic value in this series. When the cytogenetic aberrations suggested by the GCECGH (GCECGH cytogenetic subgroups) were added in the regression analysis, these GCECGH subgroups became the main prognostic indicator. Furthermore, patients older than 60 years with hemoglobin < 100 g/L and with RAEB or RAEB-t and with three or four cytopenias showed a high, early risk of death.

Taking into account the value of the prognostic

Table 3. Cytogenetic variables related to survival and leukemic transformation.

Variable	Overall survival			Leukemic transformation			
	No. of patients(%)	Median survival (yr.)	p value	No. of patients(%)	1 yr. cumulative risk (%)	5 yr. cumulative risk (%)	p value
Karyotype							
Normal	514 (49.0)	3.58	< 0.0001	72 (14.0)	15	28	< 0.0001
Abnormal	454 (51.0)	1.46		146 (35.0)	33	59	
Complex	107 (11.1)	0.50	< 0.0001	49 (45.8)	58	95	< 0.0001
Single or double	347 (35.9)	2.08		97 (28.0)	26	52	
Complex:							
5 or 7 involved	71 (66.4)	0.58	0.85	32 (45.0)	63	95	0.75
Hyperploid	6 (5.6)	0.25		3 (50.0)	65	100	
Others	30 (28.0)	0.50		14 (46.7)	60	100	
IPSS cytogenetic prognostic subgroups*							
good	556 (62)	4.38	< 0.0001	74 (13)	14	26	< 0.0001
intermediate	199 (22)	1.93		64 (32)	28	64	
poor	146 (16)	0.67		62 (43)	54	89	
Single abnormalities							
r3q21q26	6 (0.6)	2.63	0.59	3 (50)	75	100	0.05
del (5q)	55 (5.7)	4.33	0.023	11 (20)	15.5	35.5	0.02
-7/del (7q)	43 (4.4)	1.33	0.0006	14 (28.3)	41	49	0.18
-7	29 (3.0)	1.2	0.009	11 (38)	47	59	0.039
del(7q)	14 (1.4)	1.3	0.11	3 (21.4)	30	30	0.63
+8	56 (5.8)	2.08	0.37	17 (30)	24.5	62.4	0.98
r11q	13 (1.3)	3.6	0.14	4 (30.7)	19	70.5	0.57
del(11q)	7 (0.7)	3.8	0.21	1 (16)	16	50	0.23
t(11q)	6 (0.6)	2.22	0.43	3 (50)	40	92	0.60
del (12p)	13 (1.3)	NR	0.11	1 (7.7)	12.5	12.5	0.42
i(17q)	10 (1.0)	0.92	0.18	2 (20)	100	–	0.08
del (17p)	5 (0.5)	NR	0.04	0 (0)	0	0	0.15
del (20q)	13 (1.3)	5.83	0.031	1 (7.7)	20	20	0.26
+21	8 (0.8)	1.16	0.02	1 (12.5)	25	50	0.32
-Y	17 (1.8)	4.94	0.009	1 (5.9)	6	14.3	0.036
GCECGH Cytogenetic subgroups*							
Good	573 (63.6)	4.33	<0.0001	76 (13.3)	13.5	26.2	<0.0001
Intermediate	70 (7.8)	2.63		20 (28.6)	18.8	58.3	
Unknown	100 (11.1)	1.00		39 (39.6)	38.8	76.0	
Poor	158 (17.5)	0.66		65 (41.1)	53.2	82.5	

IPSS cytogenetic prognostic subgroups; good: normal, -Y, del (5q), del (20q); intermediate: +8, other single or double abnormalities; poor: complex (? 3 abnormalities) or chromosome 7 abnormalities. GCECGH (Grupo Cooperativo Español de Citogenética Hematológica) cytogenetic subgroups, good:normal,-Y,del(5q), del(11q), del(12p), del(20q); intermediate:+8, r3q21q26, t(11q), del(17p); poor: complex (?3 abnormalities), -7/del(7q), i(17q); unknown: other single or double abnormalities.
**Excluding CMML patients with WBC counts >12×10⁹/L.*

parameters (odds ratio) we proposed the new score, called the GCECGH score for OS, which allows segregation of four risk groups: low risk, intermediate risk, high risk and very high risk. According to this new score, we demonstrated a distinct prognosis for these categories (Figure 3). Table 5 shows the scoring system applied. The risk groups correlated very well with FAB subtypes (p<0.0001), since 88.5% of patients with very high risk for OS had RAEB and RAEB-t subtypes (55.7% and 32.8%, respectively). When the GCECGH score for OS was added in the regression analysis, our score was the main prognostic indicator, and only the SPS score also provided prognostic information but with a low statistical value (Table 6 and 7).

Multivariate analyses for leukemic transformation

After the three steps previously described had been applied, the IPSS cytogenetic subgroups, FAB subtypes, SPS prognostic subgroups, and hemoglobin level were the variables selected for entering the model. When the IPSS, SPS and the GCECGH cytogenetic subgroups were included in the regression procedure along with these clinical characteristics, the GCECGH cytogenetic subgroup was the second variable showing independent prognostic significance, the FAB subtype being the first.

We included these GCECGH categories in the database (attributing the points shown in Table 5) and the univariate study confirmed that each category was associated with different levels of risk of evolution to

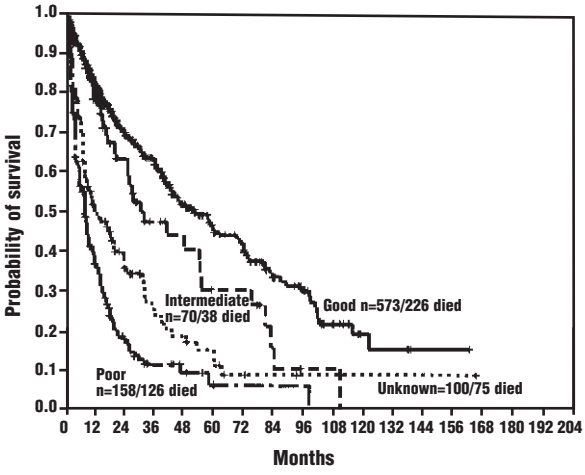

Figure 1. Survival according to GCEGCH cytogenetic subgroups. The overall log-rank, Breslow and Tarone tests were significant (p<0.0001).

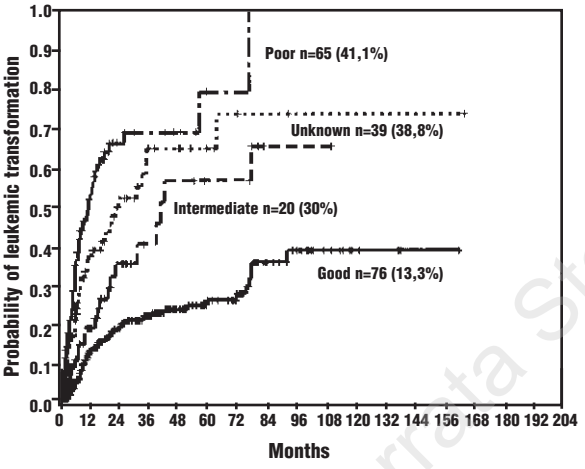

Figure 2. Leukemic risk transformation according to GCEGCH cytogenetic subgroups. The overall log-rank, Breslow and Tarone tests were significant (p<0.0001).

acute leukemia (Table 6) and correlated very well with FAB subtypes (Table 1), because all patients with very high risk for leukemic transformation had RAEB or RAEB-t (62.5% and 37.5%, respectively). When the GCECGH score for LT was added in the regression procedure, this was the main predictive factor, and only the SPS score offered a little information about this frequently fatal event (Table 8).

Discussion

The overall incidence of chromosomal abnormalities in this series of 968 patients with primary MDS was

Table 4. Prognosis of the patients with MDS according to the refined WHO subtypes.

	Overall Survival		Leukemic transformation		
	MDS patients WHO(%)	Median (years)	No. of patients (%)	1 year cumulative risk (%)	5 year cumulative risk (%)
RA	22 (10.3)	2.3	3 (13.6)	12.8	28.8
RARS	34 (15.9)	4.8	2 (5.9)	5.9	5.9
RCMD	40 (18.7)	2.3	7 (17.5)	15.5	29.3
RCMD-RS	28 (13.1)	2.7	2 (17.0)	7.7	7.7
RAEB-1	33 (15.4)	0.9	13 (39.4)	38.0	71.9
RAEB-2	34 (15.9)	0.6	11 (32.3)	45.2	–
MDS del(5q)	17 (7.9)	2.4	3 (17.5)	20.5	20.5
MDS-U	6 (2.8)	5.2	1 (17)	17	17
p value	<0.0001			<0.0001	

*MDS: myelodysplastic syndrome; WHO: World Health Organization; RA: refractory anemia; RARS: refractory anemia with ringed sideroblasts; RCMD: refractory cytopenia with multilineage dysplasia; RCMD-RS: refractory cytopenia with multilineage dysplasia and ringed sideroblasts; RAEB-1, refractory anemia with excess blasts-1; RAEB-2: refractory anemia with excess blasts-2; MDS-U: myelodysplastic syndrome-unclassified; IPSS: International Prognostic Scoring System (Greenberg et al., 1997); Int-1: intermediate 1; Int-2: intermediate 2; SPS: Spanish Prognostic Score (Sanz et al., 1989). *Excluding CMML patients with WBC counts > 12×10⁹/L.*

Table 5. GCECGH scoring system.

A. Overall survival				
Points	0	0.5	1	1.5
Years	≤60	> 60		
Hemoglobin level (g/L)	≥100	<100		
Cytopenias	0-1	2-3		
FAB subtype	RA RARS CMML	RAEB RAEB-t		
GCECGH cytogenetic subgroups*	Good	Intermediate	Unknown	Poor
B. Leukemic transformation				
Points	0	0.5	1	1.5
Hemoglobin (g/L)	≥100	<100		
FAB subtype	RARS	RA CMML		RAEB RAEB-t
GCECGH cytogenetic subgroups*	Good	Intermediate	Unknown	Poor

Cytopenias: Hb <100 g/L, neutrophils <1.5×10⁹/L, platelets <100×10⁹/L. CECGH(Grupo Cooperativo Español de Citogenética Hematológica) cytogenetic subgroups: good: normal, -Y, del (5q), del (11q), del(12p), del (20q); intermediate:+8, r3q21q26, t(11q), del(17p); poor: complex (? 3 abnormalities), -7/del7q, iso(17q); unknown: others single or double abnormalities; scores for risk groups are as follows: Low 0-0.5; Intermediate 1-1.5; High 2-2.5; Very High ≥ 3.

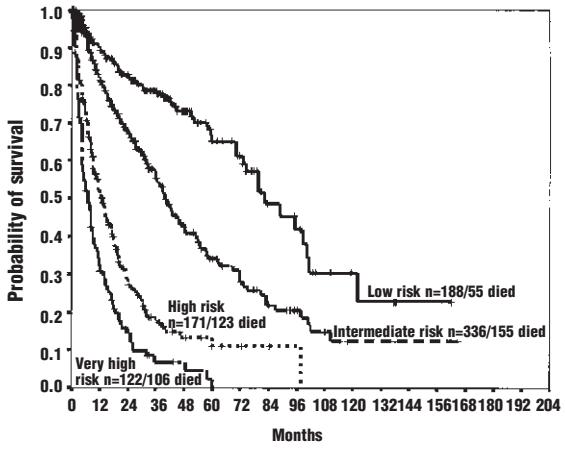

Figure 3. Survival according GCEGCH subgroups score for OS. The overall log-rank, Breslow and Tarone tests were significant (p<0.0001).

47%, similar to that in other reported series.[11-14,19,20] Our study confirms that RAEB and RAEB-t subtypes have the highest rate of chromosome abnormalities (59% and 70%, respectively), and CMML and RARS the lowest (31% and 34%, respectively).

The most common cytogenetic abnormalities found in our series were del(5q), monosomy 7/del(7q) and trisomy 8, with del(5q) being the most frequent abnormality. Other chromosomal abnormalities frequently found included del(11q), del(12p), involvement of 13q, isochromosome 17q, del(17p), del(20q), trisomy 21, monosomy 21, and loss of sex chromosomes. Chromosome loss accounts for about half of the chromosomal abnormalities in MDS. Among partial chromosome losses, del(5q) was the most common, followed by del(20q), del(11q) and del(7q).[11, 12, 19, 20] In our series, the most frequent losses were del(5q), del(7q), del(12p), del(20q), and del(11q).

Previous studies have shown the prognostic impact of chromosomal abnormalities in patients with MDS[4–7,10,19,20,26] and three large series have demonstrated by multivariate analysis that karyotype has an independent prognostic value.[12,13,19,20] There is also recent evidence that chromosomal abnormalities are the best predictors of outcome after intensive antileukemic chemotherapy.[27] Our series confirms the prognostic importance of cytogenetic findings in patients with primary MDS. The presence or absence of chromosomal abnormalities, the number of abnormalities, the IPSS cytogenetic prognostic subgroups, the GCECGH cytogenetic subgroups, and some single cytogenetic abnormalities were associated with outcome in univariate analyses.

In a series of 386 patients, Pfeilstöcker *et al.*[28] evaluated different scoring systems to assess the prognostic power of cytogenetics. Differences in prognosis were found between patients with no aberrations, those with single aberrations excluding chromosomes 7 and

Table 6. GCECGH score subgroups.

*GCECGH score for overall survival**	*No .of patients (%)*	*Median survival (yr)*	*p value*
low	188 (23.0)	6.87	< 0.0001
intermediate	336 (41.1)	3.33	
high	171 (20.9)	1.07	
very high	122 (14.9)	0.58	

*GCECGH score for leukemic transformation**	*No .of patients (%)*	*1 yr cumulative risk (%)*	*5 yr cumulative risk (%)*	*p value*
low	13 (5.0)	4.2	9.7	< 0.0001
intermediate	36 (16.2)	18.7	33.4	
high	71 (33.6)	34.0	73.8	
very high	60 (46.9)	58.5	93.0	

**Excluding CMML patients with WBC counts > 12×10⁹/L.*

Table 7. Multivariate analysis of survival.

Step	*Characteristic*	*Categories*	*expβ*	*p value*
1	GCECGH score OS subgroups*			< 0.0001
		Very high risk vs good risk	6.83	< 0.0001
		High risk vs good risk	4.46	< 0.0001
		Intermediate vs good risk	1.85	0.0001
2	SPS prognostic subgroups*			< 0.0001
		High vs low risk	2.10	< 0.0001
		Intermediate vs low risk	1.57	0.0002

*GCECGH (Grupo Cooperativo Español de Citogenética Hematológica); OS, overall survival; SPS, Spanish Prognostic Score (Sanz et al., 1989). *Excluding CMML patients with WBC counts > 12×10⁹/L. Standard 95% confidence intervals.*

Table 8. Multivariate analysis of leukemic transformation.

Step	*Characteristic*	*Categories*	*expβ*	*p value*
1	GCECGH score LT subgroups*			< 0.0001
		Very high risk vs good risk	14,06	< 0.0001
		High risk vs good risk	8,10	< 0.0001
		Intermediate vs good risk	3,39	0.0002
2	SPS* prognostic subgroups			0.0003
		High vs low risk	2,71	0.0001
		Intermediate vs low risk	1,89	0.0033

*GCECGH (Grupo Cooperativo Español de Citogenética Hematológica); LT, leukemic transformation; SPS, Spanish Prognostic Score (Sanz et al., 1989). *Excluding CMML patients with WBC counts > 12×10⁹/L. Standard 95% confidence intervals.*

8, those with aberrations on chromosomes 5, 7 or 8 and those with complex aberrations. Similar findings were observed in our series, and these results are in agreement with those found in larger series of MDS with cytogenetics.[12,13, 19-21]

One of the aims of the present study was to evaluate the prognostic accuracy of the IPSS score by multivariate analysis.[19] Our results clearly demonstrate that the IPSS is a powerful prognostic indicator in MDS patients, both for survival and risk of leukemic evolution. The prognostic impact of the most frequent cytogenetic aberrations (del5q, -7/del7q, complex karyotype, loss of Y chromosome, etc.) of MDS is very well known. Nevertheless, one possible minor pitfall of the IPSS is the inclusion of a miscellaneous number of single chromosomal abnormalities and double abnormalities in the intermediate cytogenetic prognostic subgroup. Some of the single chromosomal abnormalities might well prove to be of good or poor prognosis when a large number of cases are properly analyzed. In the present study there was some suggestion that certain chromosomal abnormalities could be segregated from the IPSS intermediate-risk cytogenetic subgroup.

Taking into account the cytogenetic abnormalities found as single anomalies, we proposed the following cytogenetic categories: *good prognosis*: normal karyotype, loss of Y chromosome, del(5q), del(12p), del(11q) and del(20q) as a single anomaly; *intermediate prognosis*: trisomy 8, rearrangemements of 3q21q26, translocations of 11q, del(17p), trisomy 18 and trisomy 19; *poor prognosis;* complex karyotypes (≥3 abnormalities), monosomy 7, deletion 7q and i(17q); and *unknown prognosis*: other single or double abnormalities. This last group includes many isolated and sometimes rare rearrangements. These new categories were studied by univariate and multivariate analyses and allowed the entities proposed by the cytogenetic subgroups of IPSS to be refined.

As regards cases with 1q involvement, this group had a poor outcome when compared with the overall series of patients by univariate analysis (median 0.66 years), and there was some trend towards a statistically significant poorer survival than that observed in the remaining cases of the IPSS intermediate-risk cytogenetic subgroup. Obviously, these results should be interpreted with caution because few patients with this anomaly were observed. In our previous report on 640 MDS cases, we found that involvement of 1q was associated with a very poor prognosis.[20] A previous report on patients with partial trisomy 1q was remarkable for the young median age of 36.5 years in this group of patient.[29] Another interesting aspect is the high prevalence of trisomy 1q in MDS from Korea.[30]

Regarding trisomy 8, a previous study that analyzed published data about trisomy 8 as a single anomaly observed that the median survival of these cases was 17.1 months (21 months for myeloproliferative disorders and 15 months for MDS).[31] This report presented a review of trisomy 8 in hematologic disorders and concluded that the incidence of trisomy 8 was higher in MDS than in myeloproliferative disorders. Interestingly, trisomy 8 was more common in women than in men and was more frequent in elderly patients.[32] In our series, trisomy 8 was more frequent in patients over 60 years old (p=0.002), and was more frequent in men (35M/21F). Taking into account the survival time (median 2.08 years) and the incidence of evolution to acute leukemia (24.5% per year) of patients with trisomy 8, this cytogenetic anomaly should be included in the intermediate category.

Regarding rearrangements of chromosome 11, trisomy 11 is a rare anomaly in acute myeloid leukemia and MDS without apparent clinical or cytological characteristics.[33] A report from Cortes *et al*.[33] concluded that 11q abnormalities define a population with a poor prognosis even when presenting *de novo*, the prognosis being worse for patients with a secondary leukemia. It is interesting to note that cases with 11q involvement also included those with a translocation involving 11q23. Among the patients with 11q abnormalities in our series, there were seven with del(11q) and six with a translocation involving 11q23, both with different overall survivals. In this series, MLL was not studied in cases with 11q23 involvement. The median survival of patients with del(11q) was longer than that of patients with a normal karyotype and very similar to that of patients with good prognosis cytogenetic abnormalities according to the IPSS (3.8 years vs 3.58 years vs 4.38 years) and their risk of transformation to acute leukemia was very similar (16% vs 15% vs 14%). Nevertheless, cases with translocations that affected 11q23 had a clinical course similar to that of cases in the intermediate risk category (median 2.22 years vs 1.93 years), and a higher incidence of evolution into acute leukemia (40% vs 28% per year). For this reason, we do not segregate these cases from the intermediate risk category. The WHO clasification is more stringent than the FAB classification regarding the percentage of blasts. Our analysis is based on the FAB classifiation which is still a very widely used classification. For this reason, cases with 11q23 rearrangement are considered MDS cases taking into account the percentage of blasts. It is worth noting that the prognosis of our cases with t(11q23) is not poor.

Concerning deletions of 12p, patients with a single del(12p) survived longer than patients with a normal karyotype and had a similar risk of leukemic evolution. The univariate analysis showed that patients with single del(12p) tended to have a prognosis resembling that of cases in the IPSS good-risk cytogenetic subgroup. 12p rearrangements have been reported in about 10% of patients with CMML, and 5% of RAEB and RAEB-t,

usually as deletions at 12p11-p13.[34] Interestingly, in our series, nine of the 13 cases with deletion 12p as a sole abnormality had RAEB-t and 53.8% (7/13) had RAEB (2.5% of all cases of RAEB). These data suggest that the better survival of cases with del(12p) was not conditioned by their association with a good prognosis FAB subtype. Abnormalities of the short arm of chromosome 12 are found in about 5% patients with acute myeloid leukemia and MDS. In a series of 59 patients with acute myeloid leukemia and MDS and 12p abnormalities, it was concluded that patients with a small deletion, del(12)(p11.2p13) have a better clinical course and patients with a large deletion, del(12)(p11.2) and additional chromosomal anomalies have a poor clinical course.[35] In our series, 12.5% of cases with del(12p) evolved into acute leukemia after 5 years and had a longer survival than patients with a normal karyotype. Taking into account our results we consider that this anomaly should be included in the cytogenetic category defined as having a good prognosis.

Loss of Y chromosome was observed in 17 cases, preferentially in patients with RA and RARS. This anomaly is observed in MDS[11,19,20] but can also be observed in older males without hematologic diseases. It is difficult to determine whether this anomaly is acquired or is present because of advanced age of the patients. In most series of MDS patients, loss of Y chromosome confers a good prognosis.[19,20] We demonstrate that the cytogenetic categories proposed by the GCECGH, in addition to FAB subtype, number of cytopenias, age and hemoglobin concentration have an independent prognostic significance in MDS patients. With these parameters, the GCECGH scores for OS and LT were superior to the remaining parameters for predicting survival and evolution to acute leukemia in our series of 968 cases. The SPS remains the best predictive score for cases with cytogenetic data.

Although we studied a large series of patients, there are many cytogenetic aberrations of unknown prognostic significance. Obviously, all these observations require confirmation in future larger studies before being accepted and used in clinical practice.

Appendix

The active members for this study were: Laboratori de Citologia Hematològica, Laboratori de Citogenètica i Biologia Molecular, Servei de Patologia, Hospital del Mar-IMAS, Barcelona. Dr. Francesc Solé, Dr. Blanca Espinet, Dra. Lourdes Florensa, Dra. Marta Salido, Servei d'Hematologia Clínica. Hospital del Mar-IMAS. Barcelona. Dr. Carles Besses, Dra. Carmen Pedro, Dra. Eugenia Abella, Dr. Antonio Salar, Dr. Sergi Serrano, Dra. Soledad Woessner, Servei d'Hematologia. Hospital Vall d'Hebron. Barcelona: Dra. Teresa Vallespí, Dr. Carlos Palacio. Servicio de Hematología. Hospital Universitario Central de Asturias. Oviedo; Dra. Elisa Luño, Dra. Carmen Sanzo, Unidad de Citogenética Centro Nacional de Investigaciones Oncológicas (CNIO), Madrid: Dr. Juan Cruz Cigudosa, Dr. Miguel Urisote, Dr. Javier Benítez, Departamento de Genética, Facultad de Ciencias, Universidad de Navarra, Pamplona; Dra. Mª José Calasanz, Dra. Mª Dolores Odero, Servicio de Genética, Hospital Universitario Puerta del Mar, Cádiz; Dr. Daniel Armenta Gil, Servicio de Hematología, Hospital General Universitario, Valencia; Dr. Felix Carbonell, Dra. Rosa Collado, Servicio de Hematología. Hospital la Fe, Valencia; Dr. Guillermo F.Sanz, Dr. José Cervera, Servicio de Genética, Hospital la Fe, Valencia; Dr. Félix Prieto, Servicio de Hematología, Hospital Clínico Universitario, Valencia; Dr. José Ángel Martínez Climent, Dra. Isana Benet, Servicio de Hematología. Hospital Universitario de Salamanca; Dr. Jesús María Hernández, Dr. Juan Luis García Hernández, Dra. Belén González, Dra. Norma Gutiérrez, Dr. Agustín Ríos, Unidad de Transplante, Hospital General Universitario Gregorio Marañón, Madrid; Dr. José Luis Díez, Nati Polo, Servicio de Genética. Fundación Jiménez - Díaz, Madrid; Dra. Esperanza Vizcarra, Unidad de Genética, Servicio de Hematología, Hospital la Princesa, Madrid; Dra. Eva Arranz, Servicio de Genética, Hospital Doce de Octubre, Madrid; Dra. Luisa Martín, Servicio de Hematología. Hospital Universitario Marqués de Valdecilla. Santander; Dra. Encarna Bureo, Dra. Marina Recio, Servicio de Hematología y Hemoterapia. Hospital Universitari Germans Trias i Pujol. Badalona (Barcelona); Dra. Isabel Granada, Dra. Fuensanta Millà, Dr. Josep Maria Ribera, Dra. Marisol Xandri.

FS contributed to the study design, data interpretation, supervised the whole study, wrote and revised the last version of the manuscript, and is primarily responsible for the paper; EL, CS contributed to the study design, data interpretation, supervised the whole study and revised the last version of the manuscript. Both authors were responsible for the statistical analyses and preparation of the tables and figures; BE, GFS, JC, MJC, FP, IG, JMH, JCC, JLD, EB, MLM, EA, RR, JAMC, MS, TV, SS, LF, SW: referred cases and revised the final version of the manuscript. The order of authorship was based on the contribution of each author to the design of the study, data interpretation and writing of the manuscript. All authors approved the version to be submitted. The authors declare that they have no potential conflict of interest.

Funding: Red de Centros de Cáncer (C03/10) and Red de Centros de Genética (C03/07) from Instituto de Salud Carlos III.

Acknowledgments: active members of the "Grupo Cooperativo Español de Citogenética Hematológica" (GCECGH) (see Appendix). Red de Centros de Cáncer (C03/10) and Red de Centros de Genética (C03/07) from Instituto de Salud Carlos III from Spanish Ministry of Health.

Manuscript received March 23, 2005. Accepted July 18, 2005.

References

1. Bennett JM, Catovsky D, Daniel MT, Flandrin G, Galton DAG, Gralnick HR, Sultan C. The French American British Co operative Group: proposals for the classification of the myelodysplastic syndromes. Br J Haematol 1985;51:189 99.
2. Jaffe ES, Harris NL, Stein H, Vardiman JW. Tumours of haematopoietic and lymphoid tissues. World Health Organization Classification of Tumours. IARC Press; Lyon. 2001.
3. Second International Workshop on Chromosomes in Leukemia 1979. Chromosomes in preleukemia. Cancer Genet Cytogenet 1980;2:108-13.
4. Knapp RH, Dewald GM, Pierre RV. Cytogenetic studies in 174 consecutive patients with preleukemic or myelodysplastic syndromes. Mayo Clin Proc 1985;60:507-16.
5. Weh HJ, Calavrezos A, Seeger D, Kuse R, Hossfeld DK. Cytogenetic studies in 69 patients with myelodysplastic syndromes (MDS). Eur J Haematol 1987; 38:166-72.
6. Musilova J, Michalova K. Chromosome study of 85 patients with myelodysplastic syndrome. Cancer Genet Cytogenet 1988;33:39-50.
7. Yunis JJ, Lobell ML, Arnesen MA, Oken MM, Mayer MG, Rydell RE, et al. Refined chromosome study helps define prognostic subgroups in most patients with primary myelodysplastic syndrome and acute myelogenous leukaemia. Br J Haematol 1988;68:189-94.
8. Nowell PC, Besa EC. Prognostic significance of single chromosome abnormalities in preleukemic states. Cancer Genet Cytogenet 1989;42:1-7.
9. Pierre RV, Catovsky D, Mufti GJ, Swansbury GJ, Mecucci C, Dewald GW, et al. Clinical cytogenetic correlations in myelodysplasia (preleukemia). Cancer Genet Cytogenet 1989; 40:149 61.
10. Suciu S, Kuse R, Weh HJ, Hossfeld DK. Results of chromosome studies and their relation to morphology, course, and prognosis in 120 patients with de novo myelodysplastic syndrome. Cancer Genet Cytogenet 1990;44:15-26.
11. Solé F, Prieto F, Badia L, Woessner S, Florensa L, Caballín MR, et al. Cytogenetic studies in 112 cases of untreated myelodysplastic syndromes. Cancer Genet Cytogenet 1992;64:12-20.
12. Toyama K, Ohyashiki K, Yoshida Y, Abe T, Asano S, Hirai H, et al. Clinical implications of chromosomal abnormalities in 401 patients with myelodysplastic syndromes: a multicentric study in Japan. Leukemia 1993; 7:499-508.
13. Morel P, Hebbar M, Lai JL, Duhamel A, Preudhomme C, Wattel E, et al. Cytogenetic analysis has strong independent prognostic value in de novo myelodysplastic syndromes and can be incorporated in a new scoring system: a report on 408 cases. Leukemia 1993; 7:1315-23.
14. Parlier V, van Melle G, Beris Ph, Schmidt PM, Tobler A, Haller E, et al. Hematologic, clinical, and cytogenetic analysis in 109 patients with primary myelodysplastic syndrome. Prognostic significance of morphology and chromosome findings. Cancer Genet Cytogenet 1994;78: 219-31.
15. Parlier V, van Melle G, Beris Ph, Schmidt PM, Tobler A, Haller E, et al. Prediction of 18-month survival in patients with primary myelodysplastic syndrome. A regression model and scoring system based on the combination of chromosome findings and the Bournemouth score. Cancer Genet Cytogenet 1995;81:158-65.
16. Morel P, Declercq C, Hebbar M, Bauters F, Fenaux P. Prognostic factors in myelodysplastic syndromes: critical analysis of the impact of age and gender and failure to identify a very-low risk group using standard mortality ratio techniques. Br J Haematol 1996; 94:116-9.
17. Mufty GJ, Stevens JR, Oscier DG, Hamblin TJ, Machin D. Myelodysplastic syndromes: a scoring system with prognostic significance. Br J Haematol 1985;59:425-33.
18. Sanz GF, Sanz MA, Vallespí T, Cañizo MC, Torrabadella M, García S, et al. Two regression models and a scoring system for predicting survival and planning treatment in myelodysplastic syndromes: a multivariate analysis of prognostic factors in 370 patients. Blood 1989;74:395-408.
19. Greenberg P, Cox Ch, Le Beau MM, Fenaux P, Morel P, Sanz G, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. Blood 1997;89:2079-88.
20. Solé F, Espinet B, Sanz GF, Cervera J, Calasanz MJ, Luño E, et al. Incidence, characterization and prognostic significance of chromosomal abnormalities in 640 patients with primary myelodysplastic syndromes. Br J Haematol 2000; 108:346-56.
21. Lee JH, Lee JH, Shin YR, Lee JS, Kim WK, Chi HS, et al. Application of different prognostic scoring systems and comparison of the FAB and WHO classifications in Korean patients with myelodysplastic syndrome. Leukemia 2003;17:305-13.
22. ISCN. An International System for Human Cytogenetic Nomenclature. F. Mitelman, ed.; S. Karger, Basel, 1995.
23. Kaplan E, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457-81.
24. Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. Cancer Chemother Rep 1966;50:163-70.
25. Peto R, Pike MC, Armitage P, Breslow NE, Cox DR, Howard SW, et al. Design and analysis of randomized clinical trials requiring prolonged observations of each patient. Br J Cancer 1977; 35:1.
26. Vallespí T, Imbert M, Mecucci C, Preudhomme C, Fenaux P. Diagnosis, classification, and cytogenetics of myelodysplastic syndromes. Haematologica 1998; 83:258-75.
27. Estey E, Keating M, Pierce S, Beran M. Application of the International Scoring System for myelodysplasia to M.D. Anderson patients. Blood 1997;90: 2843-4.
28. Pfeilstöcker M, Reisner R, Nösslinger T, Grüner H, Nowotny H, Tüchler H, et al. Cross-validation of prognostic scores in myelodysplastic syndromes on 386 patients from a single institution confirms importance of cytogenetics. Br J Haematol 1999;106:455-63.
29. Fonatsch C, Haase D, Freund M, Bartels H, Tesch H. Partial trisomy 1q. A nonrandom primary chromosomal abnormality in myelodysplastic syndromes? Cancer Genet Cytogenet 1991;56:243-53.
30. Lee DS, Kim SH, Seo EJ, Park CJ, Chi HS, Ko EK, et al. Predominance of trisomy 1q in myelodysplastic syndromes in Korea: is there an ethnic difference? A 3-year multi-center study. Cancer Genet Cytogenet 2002;132:97-101.
31. Paulsson K, Sall T, Fioretos T, Mitelman F, Johansson B. The incidence of trisomy 8 as a sole chromosomal aberration in myeloid malignancies varies in relation to gender, age, prior iatrogenic genotoxic exposure, and morphology. Cancer Genet Cytogenet 2001; 130: 160-5.
32. Collado R, Badia L, Garcia S, Sanchez H, Prieto F, Carbonell F. Chromosome 11 abnormalities in myelodysplastic syndromes. Cancer Genet Cytogenet 1999;114:58-61.
33. Cortes J, O'Brien S, Kantarjian H, Cork A, Stass S, Freireich EJ, et al. Abnormalities in the long arm of chromosome 11 (11q) in patients with de novo and secondary acute myelogenous leukemias and myelodysplastic syndromes. Leukemia 1994;8:2174-8.
34. Mauritzson N, Albin M, Rylander L, Billstrom R, Ahlgren T, Mikoczy Z, et al. Pooled analysis of clinical and cytogenetic features in treatment-related and de novo adult acute myeloid leukemia and myelodysplastic syndromes based on a consecutive series of 761 patients analyzed 1976-1993 and on 5098 unselected cases reported in the literature 1974-2001. Leukemia 2002;16: 2366-78.
35. Streubel B, Sauerland C, Heil G, Freund M, Bartels H, Lengfelder E, et al. Correlation of cytogenetic, molecular cytogenetic, and clinical findings in 59 patients with ANLL or MDS and abnormalities of the short arm of chromosome 12. Br J Haematol 1998; 100:521-33.