Genetics and Molecular Biology, 28, 4, 654-660 (2005)

www.sbg.org.br

Research Article

Cytogenetic study of Brazilian patients with Myelodysplastic Syndrome (MDS)

Tamara Borgonovo[1,2], Enilze M.S.F. Ribeiro[2], Déborah Afonso Cornélio[1], Ana Teresa Schmid-Braz[1], Valderez Ravaglio Jamur[1], Lismeri Wuicik[1], Loraine Beatriz Acosta Veiga[1], Néria A. Maia Ehmke[1], Ricardo Pasquini[3] and Iglenir João Cavalli[1,2]

[1]*Universidade Federal do Paraná, Hospital das Clínicas, Laboratório de Citogenética e Imunogenética, Curitiba, PR, Brazil.*
[2]*Universidade Federal do Paraná, Departamento de Genética, Laboratório de Citogenética Humana, Curitiba, PR, Brazil.*
[3]*Universidade Federal do Paraná, Hospital das Clínicas, Serviço de Transplante de Medula Óssea, Curitiba, PR, Brazil.*

Abstract

Bone marrow cytogenetic studies were performed on 93 patients with primary myelodysplastic syndrome (MDS) diagnosed at the Clinical Hospital of the Federal University of Paraná, Brazil. Chromosomal alterations were observed in 69% of the patients. Monosomy of chromosome 7, deletions of 7q, 5q, 12p and 20q, rearrangements of 11q23 and trisomies of chromosomes 8 and 21 were the most frequent abnormalities observed. Among adult patients the most frequent aberrations were rearrangements of 11q23 and 12p deletions. In the pediatric group, 5q deletions and monosomy of chromosome 7 were the most common alterations.

Key words: hematological disorders, myelodysplasias, cancer cytogenetics.

Received: October 24, 2003; Accepted: March 14, 2005.

Introduction

Myelodysplastic syndrome (MDS) represents a heterogeneous group of clonal disorders of hematopoietic stem cells characterized by quantitative and qualitative hematopoietic abnormalities, with cytopenia of one or more peripheral blood cell lineages but usually normal or hypercellular bone marrow (Sanz *et al*., 1989). Hematopoiesis is ineffective in one or more cell lineage, producing dyserythropoiesis, dysgranulopoiesis and dysmegakaryocytopoiesis (Goasguen and Bennett, 1992). These disorders are associated with a high risk of progression to acute myeloid leukemia (AML) and overall short survival, the death of MDS patients usually being due to cytopenia or progression to AML (Ganser and Hoelzer, 1992).

Conventionally, primary and secondary MDS are defined taking into account the previous history of the patients. According to the World Health Organization (WHO), primary MDS occurs without a known history of toxic exposure while secondary MDS is therapy-related and observed in patients with a known history of exposure to chemotherapeutic agents and/or radiation therapy (Jaffe *et al*., 2001). Although MDS occurs predominantly in older adults (median age 70 years) with a general incidence of 3 per 100,000 and reaches 20 per 100,000 over age 70 (Jaffe *et al*., 2001), MDS in children is usually more aggressive than in adults (Chan *et al*., 1997).

In order to improve the risk assessment of MDS an International Prognostic Score System (IPSS) was proposed by Greenberg *et al*. (1997), based on matched cytogenetic, morphologic and clinical data from 816 patients with primary MDS. In this system, variables were reevaluated prioritizing a more refined classification of bone marrow cytogenetic data, and three cytogenetic IPSS subgroups were recognized: good (presence of normal karyotypes, or monosomy of chromosome Y, or long arm deletions of chromosome 5 or 20); poor (presence of complex karyotypes, including three or more abnormalities, or aberrations of chromosome 7), and intermediate (presence of other chromosomal abnormalities).

Clonal chromosomal abnormalities have been reported in more than 3,000 MDS patients (Mitelman Database of Chromosome Aberrations in Cancer 2004), mainly

Send correspondence to Iglenir João Cavalli. Universidade Federal do Paraná, Departamento de Genética, Laboratório de Citogenética Humana, Caixa Postal 19071, 81531-970 Curitiba, PR, Brazil. E-mail: cavalli@ufpr.br.

adults, supporting the view that this syndrome is neoplastic *in nature*. The nonrandom distribution of the abnormalities through the different stages of MDS has helped to identify primary (pathogenetically essential for the establishment of the disease) and secondary chromosomal changes (acquired during the evolution of the disease) (Heim and Mitelman, 1995; Mitelman, 2000). Even so, further studies are still necessary for a better characterization of the frequency and nature of the chromosome aberrations in pediatric MDS (Martinez-Climent, 1997). As in the other hematological diseases, the identification of the chromosomal alterations involved in MDS is not only a powerful and essential tool for the clinical management and treatment of patients but is also central to basic research on this syndrome.

In the study described in this paper we determined the spectrum of chromosomal alterations in 93 Brazilian patients with myelodysplastic syndrome and investigated the correlation between clinical and cytogenetic findings.

Material and Methods

This study included 93 patients with primary MDS referred to the Cytogenetic Laboratory of the Clinical Hospital, Federal University of Paraná, Brazil from January 1988 to September 2002. Cytogenetic analysis of bone marrow cells was performed at the time of diagnosis. In our sample, 51 patients were male and 42 were female with a median age of 29 (range 1 to 78 years). These cases were grouped according to the French-American-British (FAB) Co-operative Group classification of Bennett *et al*. (1982) as: refractory anemia (RA), 39 patients; refractory anemia with ringed sideroblasts (RARS), 6 patients; refractory anemia with excess blasts (RAEB), 17 patients; refractory anemia with excess blast in transformation (RAEBT), 17 patients; and chronic myelomonocytic leukemia (CMML), 14 patients. The sample was subdivided into 66 adult (mean age 40.9 years range 19 to 78 years) and 27 pediatric (mean age 7.9 years, range 1 to 18) patients (Lopes *et al*., 2002).

Bone marrow cells were cultured for 24 h (Williams *et al.,* 1984) and chromosome analyses performed using a modification of the Giemsa banding technique described by Scheres (1972), the chromosomes being classified according to the International System for Human Cytogenetic Nomenclature (ISCN, 1995).

The differences among the mean values obtained from age and bone marrow blast percentage and the cytogenetic IPSS subgroups (good, intermediate and poor) were analyzed using Fisher's test and homogeneity among the variances was tested by Bartlett's test. The number of patients with different cytopenias (number of lineages involved: erythroid, granulocytic and/or megakaryocytic) in the three subgroups was analyzed by the Chi-square test. The survival curves in the cytogenetic IPSS subgroups were estimated and compared using the Kaplan-Meier method and the log rank test, respectively (Bewich *et al*., 2004).

Results

Clonal chromosome abnormalities were detected in 64 patients (69%) while 29 patients (31%) presented normal karyotypes. The frequencies of abnormal karyotypes were 74% among adults (Table 1) and 56% in children (Table 2).

Table 1 - Clinical data and karyotype of 66 adult MDS patients.

Subtype	Gender	Age (years)	Cytopenia	Evolution to AML	BM blasts (%)	BMT	Survival (months)	Karyotype
AR	F	78	2	N	< 1	N	-	46,XX,del(17)(q23)[2]/46,XX[22]
AR	M	41	2	-	0,6	N	-	46,XY[20]
AR	F	21	3	N	1	N	-	47,XX, +mar[3]/ 46,XX,del(5)(q?)[2]/46,XX[15]
AR	M	75	1	N	1	N	86 d	45,X,-Y[4]/46,XY[12]
AR	M	36	3	-	-	Y	85 a	47,XY,+8[18]
AR	F	73	1	N	2,6	N	-	44~46,X,-X[3],+4[2],del(12)(p12)[4],+mar[2] [cp4]/46,XX[10]
AR	M	65	1	N	0,1	N	54 a	46,XY,del(5)(q13q33)[10]/47,XY,idem,+21[3]/46, XY[7]
AR	F	24	-	-	-	N	-	46,XX,del(12)(p12)[4]/46,XX[16]
AR	F	31	2	N	-	Y	10 d	47,XX,+21[8]/46,XX[5]
AR	M	42	2	N	0	Y	58 a	47,XY,+8[4]/46,XY[6]
AR	M	40	1	N	< 1	Y	59 a	46,XY[20]
AR	M	26	3	N	2	Y	21 d	46,XY[30]
AR	F	25	3	N	1	Y	44 a	46~47,XX,del(11)(q23)[2],+20[2],+21[3],-22[4] [cp6]/46,XX[4]
AR	M	39	3	N	-	Y	34 d	46,XY,der(1)t(1;1)(q41;q43),der(1)t(1;1)(q41;q43) dup(1)(q21q25)[2],dup(14) (q12q32) [4][cp5]/46,XY[15]

Table 1 (cont)

Subtype	Gender	Age (years)	Cytopenia	Evolution to AML	BM blasts (%)	BMT	Survival (months)	Karyotype
AR	M	27	3	N	< 1	Y	16 d	46,XY,del(11)(q23)[4]/46,XY,-11,+mar[3]/46,XY [9]
AR	M	34	3	N	-	Y	45 a	46,XY,del(12)(p12)[2]/46,XY[14]
AR	F	45	1	N	< 1	N	6 a	46,XX [20]
AR	M	19	2	N	4	N	20 a	46,XY,inv(12)(q14q24)[5]/46,XY,idem,del(11)(q23)[2]/46,XY[13]
AR	M	54	1	N	< 1	N	28 a	46,XY[20]
AR	F	77	2	N	2	N	7 a	46,XX,del(5)(q13q33)[2]/46,XX[8]
AR	F	28	1	N	< 1	N	19 a	46,XX[20]
AR	M	63	2	N	3	N	-	45~46,XY,-Y[3],del(11)(q23)[3] [cp5]/ 46,XY[15]
AR	M	22	2	N	1	N	80 a	40~43,XY,-6[5],-7[6],-11[4],-12[4],-15[3],-16[4],-17[6],-21[3] [cp16]
AR	M	31	-	N	3	Y	4 a	46,XY,del(20)(q11)[9]/46,XY[3]
AR	F	34	1	N	0,5	N	14 a	45,X, -X [3]/46,XX[17]
AR	F	33	2	-	< 1	N	-	46,XX,del(20)(q11)[3]/46,XX[24]
AR	F	35	3	N	-	Y	5 a	46,XX[20]
AR	F	74	-	N	< 1	N	-	47,XX,+8[3]/46,XX[17]
AR	F	63	-	N	< 1	N	-	46,XX,del(11)(q23)[2]/46,XX[9]
RARS	M	68	2	-	< 1	N	-	46,XY[20]
RARS	M	47	2	N	0	Y	86 a	46,XY,t(9;11)(p23;q23)[3]/46,XY[17]
RARS	F	30	1	-	< 1	N	-	46,XX,-19[3],+mar[3]/46,XX[8]
RAEB	F	36	3	N	-	N	8 d	46,XX[20]
RAEB	M	68	2	-	6	N	-	44,XY,-17[5],-22[6] [cp10]/46,XY[6]
RAEB	F	66	1	-	14	N	-	46,XX[20]
RAEB	F	29	2	N	-	Y	2 d	46,XX[20]
RAEB	M	38	3	N	-	Y	5 d	46,XY,t(9;22)(q34;q11)[12] / 46,XY[11]
RAEB	M	24	2	Y	12	-	6 d	46,XY,del(20)(q11)[2]/46,XY[9]
RAEB	M	30	1	Y	20	Y	31 a	46,XY,del(7)(q22)[3]/46,XY[16]
RAEB	F	23	3	N	4	Y	177 a	46,XX,t(9;22)(q34;q11)[2]/46,XX[8]
RAEB	M	48	3	N	11,5	N	1 d	40~76,XY,+Y[3],+1,+1[2],+2,+2[2],+3[2],+4[2],-5[9],+6,+6[2],del(7)(q32)[5], +del(7)(q32)[3],+8[4],+9,+9[3],+10.+10[2],+11,+11[2],+12[3],+13[2],+14,+14 [2], -15[9],-16[6],-17[8],-19[3],+19[3],-21[8],-22[8],+mar1[6],+mar2[8] [cp12]
RAEB	M	67	3	N	-	-	-	45,XY,-7,del(12)(p12)[4]/46,XY[6]
RAEB	M	40	3	N	8	Y	50 d	46,XY [20]
RAEB	F	55	-	N	18	N	1 a	45,XX,-22 [3]/46,XX[17]
RAEB	F	30	2	N	11	N	-	46,XX,inv(1)(p22q24)[2]/46,XX[19]
RAEB	M	70	2	Y	-	N	5 d	46-48,XY,+7[2],+13[3],+18[2],-22[3][cp4]/46,XY [8]
RAEB	M	29	2	N	12	Y	89 a	46,XY,t(6;9)(p23;q34)[6]/46,XY[4]
RAEB	F	34	3	N	6,3	Y	19 d	46,XX,+1,der(1;7)(q10;p10)[2]/46,XX[11]
RAEBT	F	37	2	-	25	N	-	46,XX[20]
RAEBT	M	30	2	N	24	Y	12 d	46,XY,del(6)(q21)[4]/46,XY[10]
RAEBT	M	62	-	-	-	-	-	46,XY,del(12)(p12)[2] / 46,XY [18]
RAEBT	F	26	2	-	17	N	-	45,X,-X,t(8;21)(q22;q22)[9] / 46,XX [3]
RAEBT	F	20	-	-	-	-	-	46,XX,del(5)(q?)[8] / 46,XX [8]
RAEBT	M	24	3	-	15	Y	15 d	46,XY[22]
RAEBT	M	28	1	Y	16	Y	25 d	46,XY[20]
RAEBT	M	33	2	-	17	N	-	46,XY,del(11)(q23)[4]/46,XY,del(9)(q31)[2]/46,XY[14]
RAEBT	M	44	1	N	21	N	8 d	46,XY,-7,+mar[4]/ 46,XY [6]

Table 1 (cont)

Subtype	Gender	Age (years)	Cytopenia	Evolution to AML	BM blasts (%)	BMT	Survival (months)	Karyotype
RAEBT	M	33	-	Y	-	Y	20 d	47-51,XY,+4[2],+6[2],+8[2],+10[2],del(20)(q11)[2],+21[2] [cp3]/46,XY[7]
RAEBT	M	24	3	-	-	Y	12 d	46,XY,del(5)(q?)[2],del(11)(q23)[2][cp3]/46,XY[7]
RAEBT	F	29	2	N	-	Y	3 d	46,XX[20]
RAEBT	F	24	2	Y	27	N	9 d	46,XX,del(7)(q32)[2]/46,XX[18]
RAEBT	M	30	2	Y	22	N	1 d	46,XY,del(12)(p12)[3]/47,XY,idem,+9[4]/46,XY[6]
CMML	M	21	2	-	4	N	-	46,XY[20]
CMML	F	66	2	N	0,5	N	57 d	45,X,-X[3]/45,XX,-14[3]/46,XX[14]
CMML	F	27	-	-	-	-	-	46,XX,del(20)(q11)[4]/46,XX[19]
CMML	M	53	2	N	2,8	N	8 d	46,XY,del(12)(p12),del(18)(p11)[5]/46,XY[5]

Legend: M: male . Y: yes. a: alive until october/2002. BMT: bone marrow transplantation. F: female. N: no. d: died. [-]: not informed. RA: refractory anemia. RARS: refractory anemia with ringed sideroblasts. RAEB: refractory anemia with excess blasts. RAEBT: refractory anemia with excess blasts in transformation. CMML: chronic myelomonocytic leukemia.

Table 2 - Clinical data and karyotype of 27 pediatric MDS patients.

Subtype	Gender	Age (years)	Cytpenia	Evolution to AML	BM blasts (%)	BMT	Survi val (months)	Karyotype
AR	M	15	3	N	-	N	-	46,XY,del(1)(q32)[6]/46,XY[12]
AR	M	14	3	N	-	N	-	46,XY,del(5)(q14q33)[3]/46,XY[11]
AR	M	4	1	N	0	N	64 a	46,XY[20]
AR	F	7	1	N	0	N	50 a	46,XX,del(18)(p11)[2]/46,XX[13]
AR	F	2	2	N	0	Y	61 a	46,XX,add(5)(q31),del(12)(p13)[8]/46,XX[7]
AR	M	3	-	-	-	N	-	46,XY[20]
AR	F	14	3	N	-	N	11 a	46,XX[20]
AR	M	17	3	N	-	N	-	46,XY[20]
AR	M	17	2	N	3	Y	21 a	46,XY[20]
AR	F	4	2	N	1	Y	9 d	46,XX,del(6)(q21)[2]/46,XX[19]
RARS	F	5	1	N	2	Y	101 a	47,XX,del(5)(q31),+mar[8]/46,XX[4]
RARS	F	12	-	-	-	N	-	46,XX[20]
RARS	F	12	-	-	-	Y	14 d	45,X,-X[3]/46,XX,del(5)(q14q22)[3]/46,XX[14]
RAEB	F	7	1	-	5,5	N	-	46,XX[25]
RAEBT	F	7	2	Y	-	Y	15 d	47,XX,+8[3]/46,XX[10]
RAEBT	F	12	-	-	-	-	-	46,XX,del(9)(q31)[8]/46,XX[2]
RAEBT	M	14	-	Y	27	Y	26 d	45,XY,-7[5]/46,XY[11]
CMML	M	5	2	N	4,5	Y	170 a	45,XY,-7[3]/46,XY[7]
CMML	M	12	2	N	10	Y	16 d	47-48,XY,+17[3],+21[4][cp5]/46,XY[14]
CMML	F	3	1	N	-	N	28 d	38-46,XX,-4[3],-8[3],-20[3][cp15]
CMML	F	1	2	N	-	N	11 a	46,XX[20]
CMML	M	2	2	N	-	Y	25 d	46,XY[20]
CMML	M	3	2	N	-	Y	6 d	46,XY[20]
CMML	M	2	-	N	-	Y	52 a	46,XY[20]
CMML	M	1	1	N	5	Y	38 a	46,XY[24]
CMML	M	2	-	-	-	N	-	45,XY,-6[3]/46,XY[13]
CMML	F	18	2	-	2	N	-	45,X,del(X)(q24),-7[6]/46,XX[12]

Legend: M: male. Y: yes. a: alive until october/2002. BMT: bone marrow transplantation. F: female. N: no. d: died. [-]: not informed. RA: refractory anemia. RARS: refractory anemia with ringed sideroblasts. RAEB: refractory anemia with excess blasts. RAEBT: refractory anemia with excess blasts in transformation. CMML: chronic myelomonocytic leukemia.

Among chromosomally abnormal adult and pediatric cases, the most frequent chromosome abnormalities were: -7 and del(7q) (14.1%), del(5q) (12.5%), rearrangements involving 11q23 (12.5%), del(12p) (12.5%), +8 (9.4%), del(20q) (7.8%) and +21 (7.8%). Among the abnormalities detected in adults, the most frequent were rearrangements of 11q23 (16.3%), del(12p) (14.3%), -5 and del(5q) (12.2%) and -7 and del(7q) (12.2%). In the pediatric patients, del(5q) (20%) and monosomy 7 (20%) were the most frequent alterations detected. Some of the structural aberrations found in our cases involved breakpoints at 1q24, 1q32, 1q41, 1q43, 9q31 and 17q23, which have not been previously described in MDS (Figure 1).

The frequency of chromosomal alterations observed in our 93 patients was significantly higher (χ^2 = 34.01, d.f. = 6; $p < 0.001$) than that described among the MDS patients studied by Heim and Mitelman (1995) and San Miguel *et al*.(1996).

No significant differences ($p = 0.05$) were detected among the cytogenetic IPSS subgroups and the mean age ($F = 0.81$; Bartlett test: $\chi^2_2 = 0.16$, $p > 0.90$) and mean bone marrow percentage ($F = 2.58$; Bartlett test: $\chi^2_2 = 2.91$, $p > 0.20$) (Table 3). The distribution of the cytopenias (1,2 and 3) of the patients in the IPSS subgroups were: good: 10 = 1, 13 = 2 and 8 = 3; intermediate: 5 = 1, 19 = 2 and 8 = 3 and poor: 4 = 1, 5 = 2 and 5 = 3. The χ^2_4 test (3.85, $p > 0.30$) showed an homogeneous distribution within the different IPSS subgroups. The survival curves (not shown) indicated that the median survival time (a survival probability of 0.5) for the different cytogenetic subgroups were about 24 months for the good subgroup, 21 months for the intermediate subgroup and 19 months the poor subgroup. The results of the survival curves comparisons were: $\chi^2_1 = 0.02$, $p > 0.80$ (good x intermediate); $\chi^2_1 = 0.14$, $p > 0.70$ (good x poor) and $\chi^2_1 = 0.11$, $p > 0.70$ (intermediate x poor).

Discussion

We found chromosome abnormalities in the bone marrow of 69% of the 93 MDS cases analyzed, this frequency being higher than the 30 to 50% reported in the literature. The fact that most of our patients were referred to our service in a more advanced stage of the disease, when the frequency of chromosome alterations is usually high, might be an explanation for this difference. The possibility of non-referred exposure of our patients to leukemic agents could also account for the higher frequency observed. Indeed, in therapy-related MDS, higher frequencies (92%) of abnormal karyotypes are usually found (Smith *et al*., 2003).

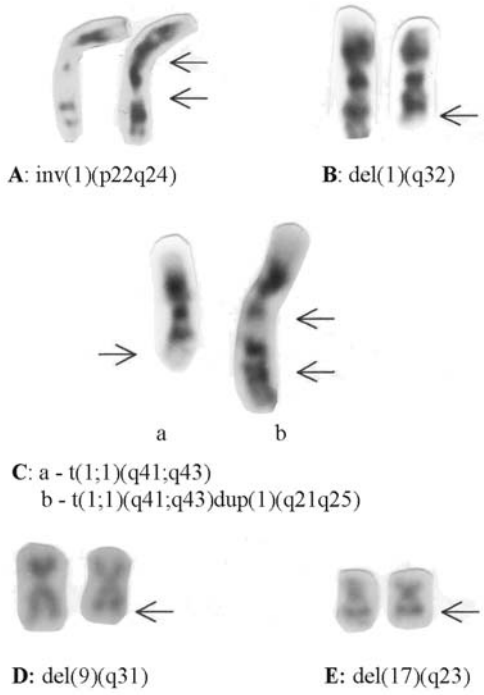

Figure 1 - Chromosome aberrations involving breakpoints at 1q24 (A), 1q32 (B), 1q41 and 1q43 (C), 9q31 (D) and 17q23 (E).

In agreement with previous reports, we observed chromosome deletions as the most frequent structural alterations, and monosomies as the most frequent numerical alterations. The most frequent abnormalities in our patients [del(7q), del(5q), del(12p), rearrangements of 11q23, +8, del(20q) and +21] have been previously described in MDS (reviewed in San Miguel *et al*., 1996; Mhawech and Saleem, 2001), but the frequencies of some of them differed from those found in the literature. For example, 11q23 and 12p rearrangements were found at a higher frequency in our study whereas 5q and 7q deletions, monosomy 7 and trisomy 8 were less frequent (Heim and Mitelman, 1995; Mhawech and Saleem, 2001). It is noteworthy that abnormalities involving 11q23 and 12p have

Table 3 - Means of age and % blasts among IPSS subgroups of MDS patients.

Parameters	IPSS subgroups					
	Good		Intermediate		Poor	
	n	mean ± SD	n	mean ± SD	n	mean ± SD
Age	37	27.86 ± 20.70	40	33.62 ± 21.57	16	33.56 ± 21.68
% blasts	22	5.28 ± 6.89	27	5.77 ± 7.64	12	10.32 ± 10.55

been reported with high frequencies in therapy-related MDS (Streubel *et al*.,1998; Bloomfield *et al*., 2002).

In our pediatric cases the frequencies of chromosome aberrations were similar to those reported in the literature. Martinez-Climent (1997) and Kardos *et al*. (2003) reported the presence of abnormal karyotypes in about 50% of their patients, with monosomy 7/del(7q) being the most frequent abnormalities. Luna-Fineman *et al*. (1995) has pointed out that, in contrast to adult cases, in pediatric patients chromosome 7 abnormalities are not frequently involved in complex karyotypes but are found as single chromosomal changes. Our findings agree with this view, in that in our sample we found that five out of eight adult patients but only one out of three pediatric cases with chromosome 7 aberrations presented this abnormality as part of a complex karyotype. Monosomy 7 is more frequently observed in pediatric MDS than in AML (Martinez-Climent, 1997; Kardos *et al*., 2003). A rapid transformation to AML is a general rule for all pre-leukemic states associated with chromosome 7 monosomy (Haas and Gadner,1996), the short survival in these cases point to the importance of detecting this chromosome abnormality at the time of diagnosis to help in the establishment of the most appropriate therapy.

The 5q deletion, which has been described as occurring at a lower frequency in pediatric MDS patients than in adults (Martinez-Climent, 1997), was unexpectedly observed at a high frequency (20%) in our cases. Chromosome 7 monosomy was also found in our cases at a frequency of 20%, although this frequency is often described for this abnormality in MDS.

The significance of individual cytogenetic aberrations in relation to prognosis deserves careful evaluation. For instance, we found chromosome 8 trisomy and 20q deletion in patients in the RA stage, which is in general agreement with the IPSS classification which includes chromosome 8 trisomy in intermediate prognosis group and 20q deletion in the good prognosis group. However, it should be borne in mind that Fernandez *et al*. (2000) have described chromosome 8 trisomy and 20q deletion in more advanced stages of the disease (RAEB and RAEB-T).

The breakpoints at 1q24, 1q32, 1q41, 1q43, 9q31 and 17q23 involved in some of the structural aberrations in our cases have not been previously described in MDS (Mitelman Database of Chromosome Aberrations in Cancer 2004; update August 23th 2004) but have been reported in other hematological diseases, such as myeloid and lymphoblastic leukemias, and may affect genes involved in the carcinogenic process, such as the *ABL2* (1q24), *TKR* (1q32), *TAL2* (9q31) and *BCAS3* (17q23) genes (OMIM, 2000). As has previously been reported in the literature, other breakpoints found in our sample and frequently involved in chromosomal aberrations in MDS co-localize with oncogenes and tumor suppressor genes which may be involved in the pathogenesis of MDS, such genes being *IRF1* (5q31), *CSF1R* (5q33.2-q33.3), *EPO* (7q21), *PLANH1* (7q21.3-q22), *MLL* (11q23) and *HCK* (20q11-q12), amongst others (Huret *et al*., 2001; OMIM, 2000).

In our study, histopathological parameters, bone marrow blast percentage and cytopenia were compared in the three cytogenetic prognosis subgroups but no significant differences were detected in spite of an increase of these parameters in the intermediate and poor cytogenetic risk groups. A possible explanation for these statistically non-significant findings could be due to the different proportions of patients submitted to bone marrow transplantation in each cytogenetic subgroup (good = 39.4%; intermediated = 47.2% and poor = 46.7%). Considering that the higher risk cytogenetic subgroups (intermediate and poor) had the higher proportion of patients submitted to BMT, we did expect an increased survival for these patients but no significant differences were observed between the survival curves for the different subgroups.

Acknowledgments

This work was partially supported by Universidade Federal do Paraná (UFPR), and Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), Brazil. The authors thank Dr. Luciane Regina Cavalli for the careful reading of the manuscript and Dr. Ives José Sbalqueiro, Marcos Euzebio Maciel and Fausto Koga de Oliveira for technical support.

References

Bennett JM, Catovsky D, Daniel MT, Flandrin G, Galton DAG, Gralnick HR and Sultan C (1982) The French-American-British (FAB) co-operative group. Proposals for the classification of the myelodysplastic syndrome. Br J Haematol 51:189-199.

Bewick V, Cheek L and Ball J (2004) Statistic review 12: Survival analysis. Critical Care 8:389-394.

Bloomfield CD, Archer KJ, Mrózek K, Lillington DM, Kaneko Y, Head DR, Dal Cin P and Raimondi SC (2002) 11q23 balanced chromosome aberrations in treatment-related myelodysplastic syndromes and acute leukemia: Report from an international workshop. Genes Chromosomes Cancer 33:362-378.

Chan GC, Wang WC, Raimondi SC, Behm FG, Krance RA, Chen G, Freiberg A, Ingram L, Butler D and Head DR (1997) Myelodysplastic syndrome in children: Differentiation from acute myeloid leukemia with a low blast count. Leukemia 11:206-211.

Fernandez TS, Ornellas MH, Carvalho LO, Tabak D and Abdelhay E (2000) Chromosomal alterations associated with evolution from myelodysplastic syndrome to acute myeloid leukemia. Leuk Res 24:839-848.

Ganser A and Hoelzer D (1992) Clinical course of myelodysplastic syndromes. Hematol Oncol Clin North Am 6:607-617.

Goasguen JE and Bennett JM (1992) Classification and morphologic features of the myelodysplastic syndromes. Semin Oncol 19:4-13.

Greenberg P, Cox C, LeBeau MM, Fenaux P, Morel P, Sanz G, Sanz M, Vallespi T, Hambcin T, Oscier D, Ohyashiri K, Toyama K, Aul C, Mufti G and Bennett J (1997) International scoring system for evaluating prognosis in Myelodysplastic Syndromes. Blood 89:2079-2088.

Haas O and Gadner H (1996) Pathogenesis, biology and management of myelodysplastic syndromes in children. Semin Hematol 33:225-235.

Heim S and Mitelman F (1995) Myelodysplastic Syndromes. Cancer Cytogenetic. 2nd edition. Wiley-Liss, New York, pp 141-163.

Huret JL, Dessen P and Bernheim A (2001) Atlas of genetics and cytogenetics in oncology and haematology, updated. Nucleic Acids Res 29:303-304.

ISCN (1995) An International System for Human Cytogenetic Nomenclature. Mitelman F (ed), S. Karger, Basel, 144 pp.

Jaffe ES, Harris NL, Stein H and Vardiman JW (Eds) (2001) World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues. IARC Press, Lyon, 351 pp.

Kardos G, Baumann I, Passmore J, Locatelli F, Hasle H, Schultz KR, Stary J, Schmitt-Graeff A, Fischer A, Harbott J, Chessells JM, Hann I, Fenu S, Rajnoldi AC, Kemdrup G, van Wering E, Rogge T, Nöllke P and Niemeyer CM (2003) Refractory anemia in childhood: A retrospective analysis of 67 patients with particular reference to monosomy 7. Blood 102:1997-2003.

Lopes LF, Lorand-Metze I, Niero-Melo L, Tone LG, Velloso E, Campanaro CM and Latorre MR (2002) The Brazilian pediatric myelodysplastic cooperative group strategies: Are they relevant to improve educational approach and correct diagnosis? Leuk Res 26:637-642.

Luna-Fineman S, Shannon K and Lange B (1995) Childhood monosomy 7: Epidemiology, biology, and mechanistic implications. Blood 85:1985-1999.

Martinez-Climent JA (1997) Molecular cytogenetics of childhood hematological malignancies. Leukemia 11:1999-2021.

Mhawech P and Saleem A (2001) Myelodysplastic syndrome: Review of the cytogenetic and molecular data. Crit Rev Oncol Hematol 40:229-238.

Mitelman F (2000) Recurrent chromosome aberrations in cancer. Mutat Res 462:247-253.

Mitelman Database of Chromosome Aberrations in Cancer (2004) Mitelman F, Johansson B and Mertens F (eds.), http://cgap.nci.nih.gov/Chromosomes/Mitelman.

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/omim/.

San Miguel JF, Sanz GF, Vallespí T, Cañizo MC and Sanz M (1996) Myelodysplastic syndromes. Crit Rev Oncol Hematol 23:57-93.

Sanz GF, Sanz MA, Vallespí T, Cañizo MC, Torrabadella M, Garcia S, Irriguible D and San Miguel JF (1989) 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 74:395-408.

Scheres VMJC (1972) Identification of two Robertsonian translocation with a Giemsa banding technique. Human Genet 15:253-256.

Smith SM, Le Beau MM, Huo D, Karrison T, Sobecks RM, Anastasi J, Vardiman JW, Rowley JD and Larson RA (2003) Clinical-cytogenetic associations in 306 patients with therapy-related myelodysplasia and myeloid leukemia: The University of Chicago series. Blood 102:43-52.

Streubel B, Sauerland C, Heil G, Freund M, Bartels H, Lengfelder E, Whandt H, Ludwig WD, Nowotny H, Baldus M, Grothaus-Pinke B, Buchner T and Fonatsch C (1998) 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 100:521-533.

Williams DL, Harris A, Williams KJ, Brosius MJ and Lemonds W (1984) A direct bone marrow chromosome technique for acute lymphoblastic leukemia. Cancer Genet Cytogenet 13:239-257.

Associate Editor: Angela M. Vianna-Morgante