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Chromosome analyses in patients with myelodysplastic syndromes: correlation with bone marrow histopathology and prognostic significance

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Summary. Chromosome analyses of bone marrow and peripheral blood cells were performed in a total of 51 patients with myelodysplastic syndromes (MDS) simultaneously with histopathological examination of resin-embedded bone marrow biopsies. Diagnosis of MDS was established by histopathology according to the French-American-British (FAB) classification, and reassessed by haematological data and clinical course. Clonal karyotypic changes were found in 30 of the 51 patients (59%): in 15 of 19 (79%) patients with refractory anaemia, 7 of 11 (64%) with refractory anaemia and excess of blasts (RAEB), 6 of 10 (60%) with RAEB in transformation, and 2 of 11 (18%) with chronic myelomonocytic leukaemia. The following three features of the histopathology revealed positive correlations with karyotype abnormalities: all cases of myelofibrosis in MDS (7/51) were accompanied by chromosome aberrations, microforms of megakaryocytes with reduced nuclear lobulation were observed in 18 of 30 cases with karyotype changes, and hypocellularity of haematopoiesis was associated with aberrations of chromosome 7 in 2 of 4 cases. No positive correlations were revealed between abnormal karyotypes and the transformation to acute leukaemia. The survival times were significantly decreased in patients with complex (3 and more) karyotype changes, when compared with patients with single (1–2) chromosome aberrations or normal karyotype, independently of the FAB classification.

Key words: Myelodysplastic syndrome – Myelofibrosis – Cytogenetics – Histopathology – Bone marrow biopsy

Introduction

The diagnosis of myelodysplastic syndromes (MDS) is often based upon the cytology of smears of bone marrow and blood, using the criteria of the French-American-British Study Group (FAB) (Bennett et al. 1982). The histopathological examination of bone marrow biopsies has been a feature of few articles dealing with the cytogenetics and prognosis of patients with MDS (Tricot et al. 1985a, b; Yunis et al. 1986; Gyger et al. 1988), though it has been recommended as an essential investigation by the Third MIC Study Group (1988). Several important findings such as the assessment of fibre increase, marrow cellularity, or the dislocation of haematopoietic cells, however, can only be determined accurately in bone marrow sections.

Correlations between the chromosomal pattern and prognosis are reported in the majority of cytogenetic studies in MDS (Jacobs et al. 1986; Yunis et al. 1986, 1988; Kerkhofs et al. 1987; Taniwaki et al. 1987, Weh et al. 1987; Billström et al. 1988; Horiike et al. 1988; Musilova and Michalova 1988; Suciu et al. 1990). Nevertheless, it is not clear which pattern of karyotypic abnormalities is associated with a shorter survival or increased tendency to leukaemogenesis in MDS.

We sought to discover in MDS any correlations between clonal karyotype changes and conspicuous histological features. We examined myelofibrosis (MF), megakaryocytic atypia and bone marrow cellularity, as well as the clinical course of the disease.

Materials and methods

For cytogenetic studies heparinized bone marrow aspirates and peripheral blood cells of the 51 patients from eight different hospitals were sent to the Cytogenetics Laboratory between 1985 and 1990. The cells were cultivated for 24 and 48 h in RPMI medium supplemented with 10% fetal calf serum. Karyotyping was performed after GTG-banding of the metaphase chromosomes, using the international system for human cytogenetic nomenclature (ISCN 1985). Chromosomal aberrations were defined as clonal if identical structural rearrangements or extra chromosomes were found in at least two cells, or, in the case of chromosome loss, in at least three cells. All cases were graded according to the number of karyotype changes into cases with one or two aberrations per metaphase and cases with complex karyotype changes involving three and more chromosomes per metaphase.

In all 51 patients, histopathological examination was performed simultaneously with the cytogenetic analyses. MDS was classified

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Table 1. Haematological and clinical findings in 51 patients with myelodysplastic syndromes. All main numbers represent the medians

FAB	*n*	Age (years)	Haemoglobin (g/dl)	Leucocytes ($\times 10^3/mm^3$)	Platelets ($\times 10^3/mm^3$)	ANLL	Survival (months)	Follow-up (months)
RA	19	72 (58–84)	9.2 (6.2–12.2)	3 (1.3–12.8)	96 (13–692)	2	19.9 (3–28)	14.9
RAEB	11	76 (52–84)	8.6 (5.6–11.1)	1.9 (1.2–7.7)	89 (19–399)	2	14.1 (3–32)	12.3
RAEB/T	10	64 (41–78)	9.3 (7.2–12.5)	1.9 (1.0–4.5)	76 (27–107)	5	4.0 (1–26)	9.5
CMMoL	11	53 (48–86)	11.1 (2.9–22.4)	9.0 (2.3–24.6)	78 (40–610)	6	10.9 (2–22)	11.9

ANLL, Acute non-lymphocytic leukaemia; CMMoL, chronic myelomonocytic leukaemia; FAB, French-American-British Study Group; RA, refractory anaemia; RAEB, RA and excess of blasts; RAEB/T, RAEB in transformation

in methacrylate-embedded bone marrow biopsies (Maschek et al. 1992) according to the criteria of the FAB co-operative study group (Bennett et al. 1982). Refractory anaemia (RA) was diagnosed in 19 cases, refractory anaemia with excess of blasts (RAEB) in 11 cases, refractory anaemia with excess of blasts in transformation (RAEB/T) in 10 cases, and chronic myelomonocytic leukemia (CMMoL) in 11 cases. The initial clinical diagnosis was MDS in 41 of 51 patients, and anaemia ($n=4$), pancytopenia ($n=3$), thrombocythaemia ($n=1$), acute leukaemia ($n=1$) or chronic myelogeneous leukaemia ($n=1$) in 10 of 51 patients, respectively. Of the 41 patients with initial clinical diagnosis of MDS, 25 had been grouped from bone marrow smears according to the FAB classification, 6 patients with RA, 9 with RAEB, 2 with RAEB/T, and 8 with CMMoL. In all patients, the clinical follow-up and haematological data were evaluated and correlated with histopathological diagnoses (Table 1). Survival was calculated from the day of the first histopathological and cytogenetic bone marrow diagnosis, and estimated by the Kaplan-Meier product-limit method. The chi-squared test was used for statistical analyses.

Results

Histopathological examination of the bone marrow biopsies revealed a FAB subtype different from the initial clinical diagnosis based upon bone marrow cytology in 12 of 25 patients. Final diagnoses were RAEB in 4 patients with an initial diagnosis of RA; RAEB/T in 5 patients with an initial diagnosis of RAEB; RA in 1 patient each with CMMoL and RAEB; and CMMoL in 1 patient with an initial diagnosis of RA.

Clonal karyotype changes (Table 2) of bone marrow cells were found in 30 of all 51 patients with MDS

Table 2. Clonal karyotype changes in 51 patients with MDS correlated to FAB subtypes

	n	Clonal	Karyotype	Changes	Total
		0	1–2	>=3	
RA	19	4	13	2	15/19 (79%)
RAEB	11	4	5	2	7/11 (64%)
RAEB/T	10	4	1	5	6/10 (60%)
CMMoL	11	9	2	0	2/11 (18%)
Total	51	21	21	9	30/51 (59%)

MDS, Myelodysplastic syndromes; for other abbreviations, see Table 1

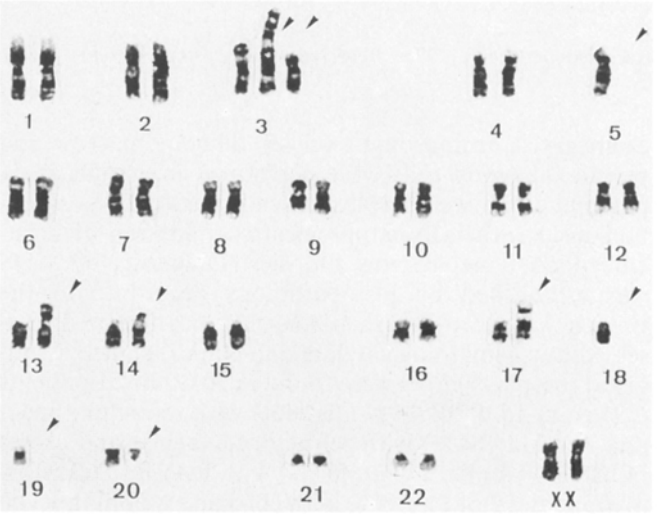

Fig. 1. Complex karyotype changes (*arrows*) of bone marrow cells in a patient with RAEB/T (case 25, Table 4)

(59%). Chromosome aberrations occurred predominantly in RA, in 15 of 19 cases (79%). Among the FAB subtypes RAEB and RAEB/T there were 7 of 11 (64%) and 6 of 10 (60%) cases with abnormal karyotypes, respectively. Most patients with CMMoL (7/9) had normal karyotypes. Despite the high incidence of chromosomal abnormalities in RA (15/19), complex karyotype changes involving three and more chromosomes per cell were only present in 2 of the 15 patients. In contrast, 5 of 6 patients with RAEB/T and chromosome abnormalities had complex karyotype changes (Table 2, Fig. 1).

When correlated with the morphological classification of MDS, some chromosome aberrations were found to be associated with the different FAB subtypes (Table 3). Deletions of 5q (6 cases), for instance, were preferentially noticed in RA (4/6), whereas monosomy 5 (5 cases) was mainly present in RAEB/T (4/5). Del(5q) as the only karyotype abnormality was noticed in 2 cases (Table 4), both exhibiting small megakaryocytes with non-lobulated round or oval nuclei in bone marrow histopathology. Three out of 4 patients with structural aberrations of chromosome 20 had RA. Translocations and deletions involving chromosome 3 were noticed in 3 cases with RAEB/T and 1 case with CMMoL.

Table 3. Specific chromosome aberrations within the FAB subtypes

FAB	del(5q)	−5	Structural aberrations	
			#3	#20
RA*	4			3
RAEB	2	1		
RAEB/T		5	3	1
CMMoL			1	

For abbreviations, see Table 1

Semi-quantitative determination of the marrow cellularity revealed hypocellularity in 4 of 51 (8%), normocellularity in 6 of 51 (12%), and hypercellularity in 41 (80%) of the 51 cases. No correlation was found between the cellularity within the bone marrow and the frequency of abnormal karyotypes. However, both patients with hypocellularity and cytogenetically abnormal bone marrow cells had aberrations of chromosome 7 (cases 9, 15, Table 4). Atypia of megakaryocytes, mainly micromegakaryocytes or megakaryocytes with multiple separated nuclei, were observed in 18 (60%) of 30 cases with abnormal karyotypes compared with 7 (33%) of the 21 cases with normal karyotypes; this difference was not statistically significant ($P=0.1$).

Reticulin fibrosis in bone marrow sections stained by Gomori's silver impregnation was observed in 7 of 51 patients, 3 cases with RA, 3 cases with RAEB/T, and 1 case with CMMoL. None of these patients showed MF with collagen fibres. All 7 patients with MDS and MF had abnormal karyotypes. In contrast, only 25 of the 45 MDS patients without MF had chromosomal abnormalities. This difference was statistically signifi-

Table 4. Cytogenetic and other findings of the 31 patients with clonal karyotype changes

Case	Age (years)	FAB	Survival (months)	Karyotype
1	72	RA	18.7	46,XY,del(20q)(q13)
2	60	RA	13.5[b]	45,XY,−7
3	75	RA	2.6	49,XX,+16,+21,+mar
4	35	RA	11.3	47,XY,+der(14)
5	68	RA[a]	2.5	45,XX,−7
6	74	RA	26.0	46,XX,t(20;22)(p11;p11)
7	68	RA	4.6	46,XX,t(13;20)(pter;q12)
8	76	RA	3.0	47,XY,+19
9	78	RA	23.0	46,XY,del(5q)(q14;q34), t(7;?)(pter;?)
10	80	RA	6.5[b]	48,XY,del(5q)(q14;q34), +2mar
11	72	RA	20.0	46,XY,del(5q)(q14;q34)
12	69	RA	18.7	45,X,−Y
13	73	RA	16.9	46,XX,inv(5)(q33–qter)
14	66	RA[a]	19.6	45–47,XX,iso(17q)
15	75	RA[a]	15.2[b]	45,XY,−7
16	79	RAEB	10.5[b]	45,XX,del(5q)(q14;q34), del(7q)(q21),−9 t(17;?)(pter;?)
17	74	RAEB	21.2	46,XY,del(4q)(q21;q28)
18	84	RAEB	23.7	46,XY,dup(11)(q13–q25)
19	75	RAEB	3.4[b]	48,XX,−5,−7,12q+,−16, +5mar
20	76	RAEB	8.1[b]	46,XY,inv(11q)(q21–q22)
21	52	RAEB	18.8	45–47,XY,+2–4mar
22	72	RAEB	80.6	46,XX,del(5q)(q13;q31)
23	78	RAEB/T	4.9[b]	46,XY,del(3p)(p11), t(3;4)(p21;pter), t(3;5)(p21;pter),−5,+mar
24	65	RAEB/T	2.5[b]	51,XX,−5,+11,+13,+21,+21, +22,+22
25	89	RAEB/T	0.9[b]	43–45,XX+t(3;3)(q25?;p25), del(3p)(p13),−5, t(13;18)(pter;pter), der(14q),17p+(t(17;19)?), −19,del(20q)(q11–qter)
26	56	RAEB/T[a]	0.1[b]	45,XY,−C
27	63	RAEB/T[a]	0.3[b]	46,XY,−C,−D,+2mar
28	65	RAEB/T[a]	3.5[b]	44–47,XX,−1,3p+(pter),−5, −6,−17,+5mar
29	66	CMMoL	9.3[b]	47,XY,+22
30	53	CMMoL[a]	10.1	46,XY,t(1;3)(p36;q21)

[a] Myelofibrosis
[b] Patient deceased

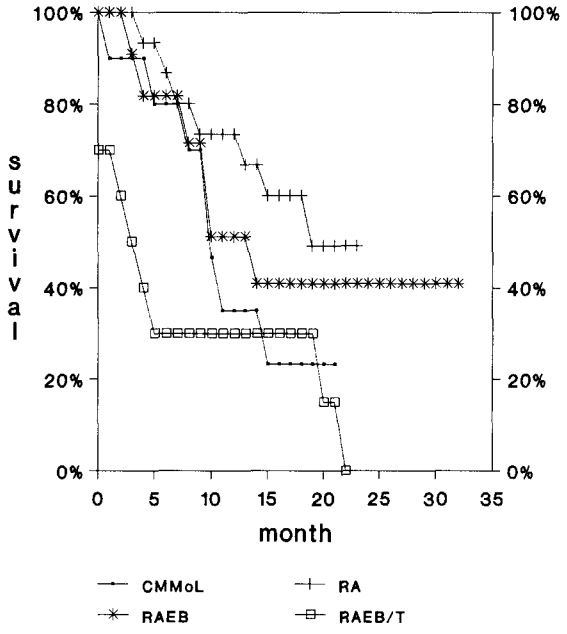

Fig. 2. Survival curves of the different FAB subtypes. The differences are nor statistically significant except for RA and RAEB/T ($P<0.004$)

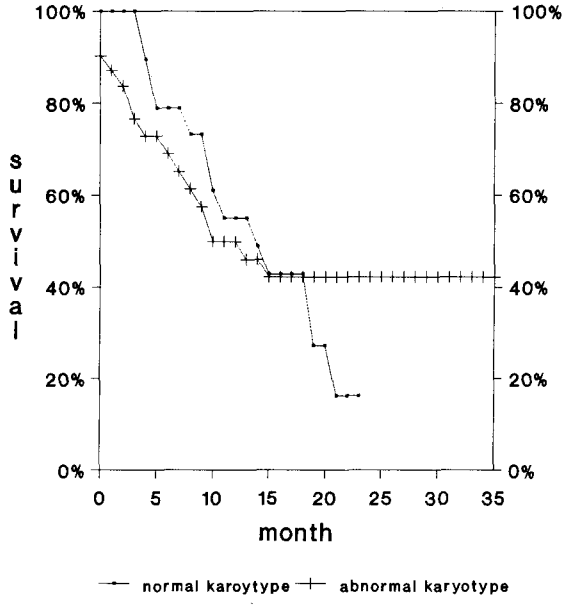

Fig. 3. Survival times in patients with cytogenetically normal bone marrow cells ($n=21$) compared to patients with clonal karyotype changes ($n=30$). No statistically significant differences between the two curves ($P=0.48$)

cant ($P<0.05$). Complex karyotype changes were noticed in 2 of 7 cases with MF (Table 4). The patient with CMMoL and MF had a 1:3 translocation (p36; q21) that was associated with a striking hyperplasia of megakarypoiesis and high platelet count (1.800×10^9/l).

The clinical course of the patients revealed that 15 of 51 (29.4%) developed acute non-lymphocytic leukaemia, 2 of 17 patients with RA, 2 of 9 patients with RAEB, 5 of 10 patients with RAEB/T, and 6 of 11

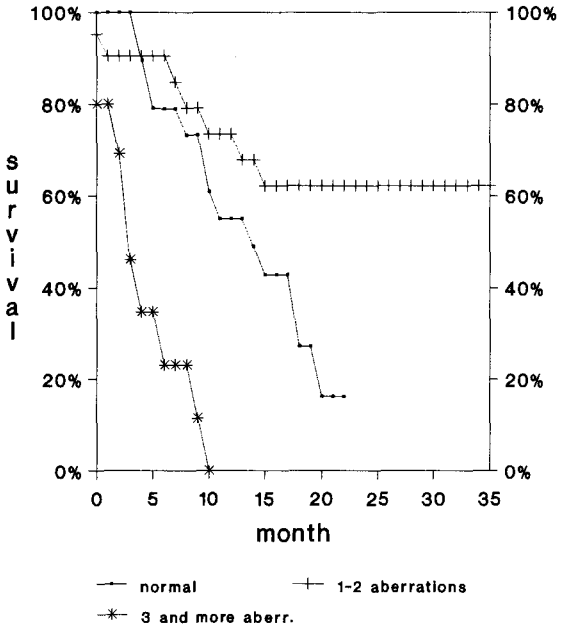

Fig. 4. Comparison of survival times between patients with normal chromosome pattern, patients with 1–2, and patients with more than 3 (complex) karyotype changes. Survival is significantly shorter in patients with complex karyotype changes compared with patients with 1–2 chromosome aberrations ($P=0.0009$) or normal karyotypes ($P=0.0014$). The differences between patients with normal karyotype or 1–2 karyotype changes are not significant ($P=0.2318$)

patients with CMMoL. No correlation was found between karyotype changes and transformation into acute non-lymphocytic leukaemia.

Of the 51 patients included in this study, 30 had died. Among all FAB subgroups the longest median survival time was observed in patients with RA (19.9 months). Patients with RAEB, RAEB/T, and CMMoL had median survival times of 14.1 months, 4.0 months, and 10.9 months, respectively. Significant differences in the survival curves among the FAB subtypes (Fig. 2) were noticed only between RA and RAEB/T ($P<0.004$).

The results of karyotype analyses were correlated to the survival times of the MDS patients. No discrepancy in the survival was observed between the 21 patients with cytogenetically normal bone marrow cells (Fig. 3) and the 30 patients with clonal karyotype changes ($P=0.48$). The survival time of patients with complex chromosome abnormalities, however, was significantly decreased compared to those patients with normal karyotype ($P=0.0014$) or only one or two chromosome abnormalities ($P=0.0009$) (Fig. 4). The differences between patients with normal karyotype and one or two karyotype changes were not statistically significant ($P>0.2$).

Discussion

The percentage of clonal karyotype changes found in MDS (59% among 51 patients) is comparable to most other studies (Weh et al. 1987; Horiike et al. 1988; Musilova and Michalova 1988). This singular prevalence of

cytogenetic abnormalities in RA, a finding in contrast to the majority of previous reports (Taniwaki et al. 1987; Weh et al. 1987; Billström et al. 1988; Gyger et al. 1988; Musilova and Michalova 1988) may be due to the relatively small number of cases within the other FAB subgroups. MDS was not considered the initial clinical diagnosis in 10 of 51 patients. Moreover, in 12 of 25 cases initially classified cytologically histopathological evaluation of bone marrow sections revealed a different FAB subtype. In these cases, examination of the bone marrow biopsy was decisive in the final diagnosis confirmed by clinical follow-up. Discrepancies in the determination of the percentage of marrow blasts in cytology and biopsy specimens have also been reported and may be due to technical problems of aspiration (Delacretaz et al. 1987).

The relationships between karyotypic abnormalities and the histopathological features of bone marrow are interesting. All of our 7 MDS patients with MF had cytogenetic abnormalities, supporting the recent results of Ohyashiki et al. (1991), who found an incidence of 6 of 7, and multiple chromosome abnormalities occurring in 4 patients. These data contrast with the study of Pagliuca et al. (1989), who described chromosomal abnormalities in only 1 of 6 MDS patients with MF. Only 2 of our 7 patients displayed complex karyotype changes which were correlated with reduced survival. Two of the remaining 5 patients had a monosomy 7, and another patient had a 1;3 translocation. Both abnormalities have been reported to be associated with a bad prognosis in MDS patients (Moir et al. 1984; Yunis et al. 1986). At present it is not clear whether MDS with MF represents a distinct entity with poor prognosis (Del Potro et al. 1989; Pagliuca et al. 1989; Lambertenghi-Deliliers et al. 1991; Ohyashiki et al. 1991; Maschek et al. 1992).

Severe atypia of megakaryopoiesis was found in a high proportion of our MDS patients with abnormal karyotypes. Dysmegakaryopoiesis is also reported to be correlated with a poor prognosis, and has been associated with the development of MF in MDS (Pagliuca et al. 1989; Rios et al. 1990; Maschek et al. 1992). Deviations of the megakaryocytic cell line in patients with del(5q) or a 1;3 translocation involving 3q21, as observed among our patients, have also been reported earlier (Mahmood et al. 1979; Moir et al. 1984; Van den Berghe et al. 1985).

Few MDS patients with marrow hypocellularity have been examined cytogenetically, and abnormalities of chromosome 7 have been described in some of those cases (Dezza et al. 1983; Nand and Godwin 1988; Motoji et al. 1990). This finding is supported by our results, since in both patients with conspicuous hypoplasia of haematopoiesis and karyotype changes an abnormality of chromosome 7 was revealed. Patients with complex karyotype changes had a worse clinical course compared with patients with cytogenetically normal bone marrow cells or single chromosome aberrations. This affects life expectancy in particular; it was reduced significantly. Few earlier reports have emphasized the significance of complex karyotype changes in the prediction of prognosis in MDS (Billström et al. 1988; Horiike et al. 1988; Musilova and Michaelova 1988; Suciu et al. 1990). In patients with RAEB/T complex karyotype abnormalities have been associated with failure of response to chemotherapy (Michels et al. 1989). There were slight differences in the survival curves between our patients with normal karyotypes and patients with single changes, which, however, were not significant. These differences may be explained by the presence of patients with del(5q) within the group of patients with single aberrations which are known to have a more favourable prognosis (Mahmood et al. 1979; Van den Berghe et al. 1985; Billström et al. 1988). The transformation of MDS into acute leukaemia, which occurs in between 20% and 45% of the patients in larger collections (Tricot et al. 1985a; Sanz et al. 1989) is not considerably influenced by cytogenetic abnormalities as shown by these results and the results in the literature (Weh et al. 1987; Billström et al. 1988; Gyger et al. 1988).

In conclusion, MF reveals the strongest correlation with cytogenetic abnormalities as shown here and described recently by Ohyashiki et al. (1991). Whether these chromosomal aberrations are dependent on or induce the MF needs further study. However, both are correlated with a poor clinical course in the patients (Maschek et al. 1990, 1992; Ohyashiki et al. 1991). Further correlations may be revealed between abnormalities of karyotype and atypia in megakaryopoiesis, and between aberrations of chromosome 7 and hypoplastic haematopoiesis. Patients with complex (3 and more) karyotype changes had a significantly shorter survival than patients with normal karyotype ($P=0.0014$) or single (1–2) chromosome aberrations ($P=0.0009$), a finding independent of the FAB classes of MDS.

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