

Key words: acute non-lymphocytic leukaemia; chromosomes-myelodysplastic syndromes-survival

Cytogenetics of the myelodysplastic syndromes

Georg H. Borgstrom
Department of Medical Genetics, University of
Helsinki, Helsinki, Finland

Chromosome aberrations occur in 30—50 % of patients with myelodysplastic syndromes (MDS). Chromosome aberrations found in MDS are generally found in acute non-lymphocytic leukaemia (ANLL), while certain aberrations of ANLL do not occur in MDS. The clinical significance of these aberrations has been evaluated on the basis of several series from literature and a large series from Helsinki University Central Hospital. The presence of an aberrant clone with major karyotypic aberration (MAKA) or monosomy 7 in a patient with MDS indicates a higher risk of transformation to acute leukaemia and a shorter survival.

Acquired chromosomal aberrations occurring clonally are generally considered to be a sign of a malignant or premalignant state. Thus the fact that patients with myelodysplastic syndromes (MDS) have aberrations in their bone marrow cells is compatible with the neoplastic nature of these disorders. In leukaemias certain cytogenetic aberrations correlate with prognosis and with specific haematological features, thus being of clinical significance. Clonal evolution often marks a change to a more malignant form of leukaemia. Consequently, it is relevant to ask whether such correlations exist in the myelodysplastic syndromes and whether chromosome analysis can be used in monitoring and evaluating these disorders.

The literature on cytogenetics in the myelodysplastic syndromes is difficult to interpret due to varying nomenclature and the different criteria used for the inclusion of cases. Only in a few reports the patients have been classified according to the FAB-proposals (1). The present review is based on several large series and some unpublished data from Helsinki University Central Hospital (2—5, 10, Todd & Pierre and Bloomfield, in this number).

Cytogenetic findings

The incidence of chromosomal aberrations in MDS varies between 32 % and 51 % (Table 1). This variation could be explained by the different cytogenetic techniques as well as by the diagnostic criteria for the MDS. From a diagnostic point of view, the presence of an aberrant clone confirms the diagnosis of MDS while a normal result does not exclude this possibility.

The most common aberrations in MDS are also found in *de novo* ANLL (-5,5q-, -7,7q-, -8, +19,20q-)(3). On the other hand, some of the most characteristic translocations of acute non-lympho-

TABLE 1
Frequency of chromosome aberrations in the myelodysplastic syndromes

Source	Total	Abnormal clones (%)	Normal karyotype
2nd International Workshop (3)	244	125 (51)	119
Nowell et al (2)	80	31 (39)	49
Ayraud et al (4)	88	28 (32)	60
Teerenhovi et al (5)	158	81 (51)	77

1986.012

cytic leukaemia (ANLL), i.e. ANLL M2 and t(15;17)(q22;q12) not found in *de novo* MDS. In some leukaemias pass through phase with characteristic chromosomal aberrations while others develop "directly".

Certain aberrations correlate with myelodysplastic syndromes, appear after treatment (Bloomfield, in this number), 5q- and -5, and 7q- and -7. They also appear in primary MDS.

Among recurring numerical aberrations trisomy 8 and trisomy 19 are especially characteristic of the long arm of chromosome 19. They have been found in MDS but also in ANLL (3, 6). In our series as well as in Bloomfield and Bagby (10) deletion at q14 has been found in several patients with MDS but also a recurring breakpoint in chromosome 19 in this number. Only a few recurrent translocations have been described in MDS, t(1;7) and t(1;7) which results in a partial monosomy 7 (8). Some patients present with major karyotypic aberrations, i.e. they have 3 or more karyotypic aberrations in the same clone. In addition, several patients reported only in a single patient have been found in MDS.

Clinical correlations with chromosome aberrations

For the evaluation of the clinical significance the Helsinki series was grouped according to the common aberrations: 5q-, -7,

TABLE 2
Morphological classification of certain FAB-groups

FAB-group	Normal
RA	21
RARS	22
RAEB	19
CMML	11
RAEBt	4
Total	77

RA = refractory anaemia, RARS = refractory anaemia with ringed sideroblasts, CMML = chronic myelomonocytic leukaemia.
* FAB-classification not available for

myelophytic leukaemia-
myelodysplastic syndromes-survival

Myelodysplastic syndromes

Genetics. University of
and

o-
n-
S.
ral
he
ny
ia

S

chromosomal aberrations in MDS
and 51 % (Table 1). This variation
is determined by the different cyto-
genetic as well as by the diagnostic
criteria. From a diagnostic point of
view, an aberrant clone confirms
the diagnosis and a normal result does
not exclude the possibility.

Aberrations in MDS are
characteristic of ANLL (-5,5q-, -7,7q-, +8,
and others). On the other hand, some of the most
common aberrations of acute non-lympho-

cytic leukaemia (ANLL), i.e. t(8;21)(q22;q22) in
ANLL 412 and t(15;17)(q22;q12) in ANLL M3, are
not found in *de novo* MDS. This could indicate that
some leukaemias pass through a preleukaemic
phase with characteristic chromosome aberrations
while others develop "directly".

Certain aberrations correlate to secondary mye-
lodysplastic syndromes, appearing after prior can-
cer treatment (Bloomfield, in this number), name-
ly 5q- and -5, and 7q- and -7. They can, however,
also appear in primary MDS.

Among recurring numerical aberrations, triso-
my 8 and trisomy 19 are especially notable. Dele-
tion of the long arm of chromosome no. 20 has
been found in MDS but also in polycythaemia vera
(3, 6). In our series as well as in the series of An-
derson and Bagby (10) deletion of chromosome 11
at q14 has been found in several patients. This is
also a recurring breakpoint in ANLL (Bloomfield,
in this number). Only a few recurring translocations
have been described in MDS. Of note are t(2;11)
(7) and t(1;7) which results in a partial trisomy 1
and a partial monosomy 7 (8). Some MDS patients
present with major karyotypic aberrations (MAKA),
i.e. they have 3 or more karyotypic aberrations in
the same clone. In addition, several aberrations re-
ported only in a single patient have been described
in MDS.

Clinical correlations with chromosome groups

For the evaluation of the clinical correlations the
Helsinki series was grouped according to the most
common aberrations: 5q-, -7, +8, MAKA, other

aberrations and cases with only normal mitoses in
the bone marrow (BM). The distribution of the
FAB-subtypes of MDS in the different chromo-
some groups is presented in Table 2. No significant
difference was found which is of interest in view
of the differences in survival among the groups
noted below.

Among haematological parameters, the presence
of blasts in the blood and the increase in the per-
centage of blasts in the bone marrow, respec-
tively, were studied (Tables 3 and 4). The MAKA group
had blasts in the blood more often than the other
cytogenetic groups (38 % vs. 10-13 %) and this
difference was statistically significant ($p < 0.05$).
There was no significant difference in the chromo-
somal aberrations in patients with < 5 % vs.
 > 5 % of blasts in the BM.

Correlations of cytogenetics to specific haema-
tological features have been sought for and found,
at least, for one aberration. Among MDS there is
an entity called the 5q- syndrome with the same
chromosomal marker as in some secondary mye-
lodysplastic syndromes, an interstitial deletion of
the long arm of chromosome 5, but, in these pa-
tients, a prior exposure history is lacking. The 5q-
syndrome is a distinct clinico-haematological enti-
ty which occurs in elderly females (Van den Berghe,
in this number) and includes refractory macrocytic
anaemia, normal platelet count, a normal or low
number of erythroid precursors in the BM and hy-
polobulation of megakaryocytes. The clinical
course is benign as compared to patients with
secondary myelodysplastic syndromes. In patients

TABLE 2
Morphological classification of certain chromosome groups according to the FAB-criteria

FAB-group	Normal	5q-	other	+8	-7	MAKA	Total
Ri	21	4	7	4	4	4	44
RARS	22	0	17	2	0	4	40
RAEB	19	6	8	1	3	6	43
CMML	11	0	7	1	1	0	15
RAEBt	4	0	2	0	0	2	8
Total	77	10	31	8	8	10	150*

RA = refractory anaemia. RARS = refractory acquired sideroblastic anaemia, RAEB = refractory anaemia with excess of blasts.
CMML = chronic myelomonocytic leukaemia. RAEBt = refractory anaemia with excess of blasts in transformation.

* FAB-classification not available for 8 pts.

aberrations in the myelodysplastic

Total	Abnormal clones (%)	Normal karyotype
244	125 (51)	119
80	31 (39)	49
88	28 (32)	60
158	81 (51)	77

TABLE 3
Blasts in peripheral blood*

Blasts in PB	Percent of each cytogenetic group					
	Normal (n = 78)	5q- (n = 10)	other (n = 38)	- 8 (n = 8)	- (n = 8)	MAKA (n = 16)
No	90	90	87	87	87	62
Yes	10	10	13	13	13	38

* Data from Teerenhovi et al (5)

TABLE 4
Presence of blasts in the bone marrow in the different chromosome groups (%)

% blasts in BM	Normal	5q-	other	- 8	-	MAKA	Tau
< 5	40	64	67	86	62	56	hi
> 5	60	36	33	14	38	44	3*

* Data from Teerenhovi et al (5)

with 5q- syndrome the chromosome abnormality appears as the sole aberration while in those with secondary MDS it is usually accompanied by other aberrations. Our experience is that the 5q- syndrome can be separated from the other forms of MDS using the four haematological features mentioned above (9).

An essential question is whether there is a difference in the course of the disease between patients with a chromosome aberration in the bone marrow cells and patients with normal karyotype. This has been evaluated at the Second International Workshop on Chromosomes in Leukemia (3). Patients without an aberration showed a lower frequency of development of ANLL than those with only abnormal cells or those with a mixture of normal and abnormal cells. This has also been found in the series of Todd and Pierre (in this number), Nowell et al (2) and Ayraud et al (4). In our series there was a tendency towards this direction, but the difference was not statistically significant (Table 5). However, when the cytogenetic subgroups were analyzed, the patients with MAKA and monosomy 7 tended to have a higher likelihood to develop acute leukaemia (Table 6). This is in line with the findings of Anderson and Bagby (10).

The overall survival evaluated in our material with regard to the chromosome groups is presented

in Table 7. At present there is no significant difference in survival among patients with normal or abnormal karyotype (Kaplan-Xleier product limit survival method, $p = 0.06$). This is in contrast to

TABLE 5
Chromosomes as predictor of acute leukaemia

Source	Number (%) of cases developing ANLL		
	Total	Abnormal clones	Normal karyotype
2nd International Workshop (3)	244	44 (27)	19 (15)
Nowell et al (2)	80	25 (81)	18 (37)
Ayraud et al (4)	88	22 (78)	12 (20)
Teerenhovi et al (5)	149	24 (33)	17 (22)

TABLE 6
Development of leukaemia in the different chromosome groups

Group	Total	Yes	No	% leukaemia
Normal	77	17	60	22
5q-	10	1	9	10
Other	31	11	20	35
+ 8	8	2	6	25
-	7	3	4	43
MAKA	16	7	9	44
Total	149*	41	108	27

* Data not available for 9 pts.

TABLE 7
Survival in certain chromosome groups

Group	Total	Dead
Normal	76	51
5q-	10	3
Other	31	25
+ 8	8	4
-	7	1
MAKA	16	15

the findings of Todd and Pierre who found survival significantly better with normal karyotype. However, MAKA or monosomy 7 had a poor survival compared to all the other patients ($p < 0.01$). In our series there was not a significant difference in survival between the FAB-groups in the different chromosome groups, and, thus, the survival was not affected by a difference of the stage of disease.

Conclusions

Chromosome aberrations occur in 17% of patients with myelodysplastic syndrome.

Chromosome aberrations found in MDS are generally found in ANLL, while 10% of ANLL do not occur in MDS.

At least one aberration of MDS predicts a specific clinical picture, the 5q- syndrome.

The presence of certain chromosome aberrations (MAKA and monosomy 7) predicts development of leukaemia and shorter survival.

TABLE 7
Survival in certain chromosome groups

Group	Total	Dead	Alive	% Alive
Normal	76	51	25	33
5q-	10	3	-	70
Other	31	25	6	19
MAKA	8	4	4	50
-	-	-	0	0
MAKA	16	15	1	6

the findings of Todd and Pierre (in this number) who found survival significantly longer for patients with normal karyotype. However, our patients with MAKA or monosomy 7 had a poorer survival than all the other patients ($p < 0.01$). It is notable that there was not a significant difference in the distribution of the FAB-groups in the different cytogenetic groups, and, thus, the survival is not a reflection of a difference of the stage of the MDS.

conclusions

Chromosome aberrations occur in about 30–50 % of patients with myelodysplastic syndromes.

Chromosome aberrations found in MDS are generally found in ANLL, while certain aberrations of ANLL do not occur in MDS.

At least one aberration of MDS is connected with a specific clinical picture, the 5q- syndrome.

The presence of certain chromosome aberrations (MAKA and monosomy 7) predicts the development of leukaemia and shorter survival.

References

1. Bennett JM, Catovsky D, Daniel MT, et al. Proposals for the classification of the myelodysplastic syndromes. *Br J Haematol* 1982; 51: 189–99.
2. Nowell PC. Cytogenetics of preleukemia. *Cancer Genet Cytogenet* 1982; 5: 265–78.
3. Second International Workshop on Chromosomes in Leukemia. Chromosomes in preleukemia. *Cancer Genet Cytogenet* 1980; 2: 108–13.
4. Ayraud N, Donzeau M, Raynaud S, Lambert J-C. Cytogenetic study of 88 cases of refractory anemia. *Cancer Genet Cytogenet* 1983; 8: 243–48.
5. Teerenhovi L, Borgstrom GH, Lintula R. Clinical significance of cytogenetics in myelodysplastic syndromes. Unpublished.
6. Mitelman F. Catalogue of chromosome aberrations in cancer. *Cytogenet Cell Genet* 1983; 36: 4–515.
7. de la Chapelle A, Knuutila S, Elonen E. Translocation (2;11)(p21;q23) in acute non-lymphocytic leukaemia. A non-random association. *Scand J Haematol* (in press).
8. Borgstrom GH, Bloomfield CD, de la Chapelle A. Translocation 1;7 with resulting monosomy 7q and trisomy 1q; a common recurring abnormality in myelodysplastic syndromes. *Cytogenet Cell Genet* 1985; 40: 584.
9. Teerenhovi L, Borgstrom GH, Lintula R, Elonen E, Knuutila S, Vuopio P. Specificity of some haematological features for 5q- chromosome in preleukemic patients. Meeting abstract. Sixth Meeting of the International Society of Haematology, European and African Section. 1981. Athens, Greece.
10. Anderson RL, Bagby GC Jr. The prognostic value of chromosome studies in patients with the preleukemic syndrome (Hematopoietic dysplasia). *Leuk Res* 1982; 6: 175–81.

Correspondence:
G. H. Borgstrom,
Department of Medical Genetics
Haartmaninkatu 3,
SF-00290 Helsinki,
Finland

	MAKA (n = 16)	Total (n = 158)
1	62	87
3	38	13

	MAKA	Total
1	56	63
3	44	37

ent there is no significant difference among patients with normal or 5q- (Kaplan-Meier product limit = 0.06). This is in contrast to

Development of acute leukaemia

	Number (%) of cases developing ANLL		
	Total	Abnormal clones	Normal karyotype
1	244	44 (27)	19 (15)
2	80	25 (81)	18 (37)
3	88	22 (78)	12 (20)
4	149	24 (33)	17 (22)

Survival in the different chromosome groups

	Yes	No	% leukaemia
1	17	60	22
2	1	9	10
3	11	20	35
4	2	6	25
5	3	3	43
6		9	44
7	41	10X	26

pts