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Karyotype in Multiple Myeloma and Plasma Cell Leukaemia

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Between October 1988 and October 1991, 104 patients with multiple myeloma and 6 with plasma cell leukaemia were studied cytogenetically. Abnormal karyotypes were found in bone marrow cells of 33 patients (30%). Most pathological karyotypes were complex with numerous modal and structural anomalies. Numerical anomalies most frequently involved chromosome 11 and structural aberrations occurred most often in chromosomes 1, 11 and 14. The most consistent structural aberration was a 14q+ chromosome (10 patients) resulting from a t(11;14)(q13;q32) in 4 patients and a t(8;14)(q24;q32) in 1 patient. Sequential cytogenetic studies were performed in 15 patients. In 5 of 8 cases with a normal karyotype at diagnosis, chromosomal anomalies were detected when disease progressed. In concomitant cytogenetic/cytological studies it was found that in the majority of patients with normal karyotype the mitoses originated from contaminating normal bone marrow cells. Pathological karyotypes were detected more frequently in pretreated than in untreated patients, in patients with plasma cell leukaemia than in patients with multiple myeloma, in patients with stage III and dense bone marrow infiltration than in patients with stage I. Patients with abnormal karyotype, irrespective if pretreated or not, had a significantly shorter median survival than those with normal karyotype. These findings suggest that karyotype is an independent prognostic factor in multiple myeloma.
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INTRODUCTION

INVESTIGATIONS INCORPORATING chromosome analyses have been relatively rare in multiple myeloma and plasma cell leukaemia as compared with chronic myeloid and acute myeloid and lymphatic leukaemias. The main reason for this lack of cytogenetic information lies in the low proliferation rate of plasma cells *in vitro* and hence in a low number of mitoses that can be analysed. In the few reported studies [1–8] the chromosomal aberration rate was about 40% with t(8;14)(q24;q32) and t(11;14)(q13;q32) being the most frequent

anomalies. The clinical significance of an abnormal karyotype has not been well documented, but seems to bear a poor prognosis [4–8].

The aim of this cytogenetic study of 110 patients with multiple myeloma and plasma cell leukaemia was to evaluate the chromosomal aberration rate in these diseases and to find correlations with clinical parameters and prognosis.

PATIENTS AND METHODS

Patients

Patients' characteristics are given in Table 1. Most patients were treated according to BMFT protocol MM02 [10]. Patients in stage III and progressive stage II were randomised to receive either melphalan/prednisone or VBAMDex (vincristine, BCNU, doxorubicin, melphalan, dexamethasone) chemotherapy. The percentage of bone marrow infiltration by plasmocytes was counted on cytological slides.

Cytogenetic analysis

Chromosome analysis was performed according to standard techniques. Bone marrow cells were cultured in RPMI-1640 medium with 15% fetal calf serum for 72 and 96 h. Interleukin-6 (25 U/ml) was added to the culture. G-banding was performed following Seabright's technique [11]. Concomitant cytogenetic/cytological examination of mitoses was done as described by Berger *et al.* [12]: an aliquot of the cell suspension was withdrawn after the colchicine treatment just prior to the hypotonic shock, spun onto glass slides with a cytocentrifuge and stained with May-Grünwald-Giemsa. Mitoses of plasma cells could easily be differentiated from those of contaminating bone marrow cells by a basophil or flamed cytoplasm of plasma cells.

Statistical analysis

For statistical analysis χ^2 tests were used [13]. Survival curves were established by the method of Kaplan and Meier [14]. Statistical differences between life table curves were calculated by the log-rank test [15]. Factors of independent prognostic value were determined by multivariate analysis according to the Cox model [16].

RESULTS

Cytogenetic findings

Chromosome analysis revealed abnormal karyotypes in bone marrow samples of 33 of 110 patients (30%) with multiple myeloma or plasma cell leukaemia. Most pathological karyotypes were complex with numerous modal and structural anomalies. Karyotypes were hypodiploid in 4 patients, pseudodiploid in 6 patients, hyperdiploid in 16 patients, near triploid in 4 patients and near tetraploid in 3 patients.

Chromosome 11 was most often involved in numerical aberrations, but almost all chromosomes showed losses and gains (Fig. 1). Chromosomes 1, 11 and 14 were most frequently involved in structural aberrations (Fig. 2). The break points of chromosome 1 were distributed quite equally, although 1p13, 1q12, 1q21 and 1q23 showed slight preponderance (Fig. 3). On chromosomes 11 and 14 break points were remarkably clustered at 11q13 and 14q32 (Fig. 3).

The most consistent structural aberration was a 14q+ chromosome found in 10 patients. In 4 cases this resulted from a t(11;14)(q13;q32). 1 patient with a plasma cell leukaemia had a t(8;14)(q24;q32), and in 5 cases the origin of the additional material could not be assigned. Further chromosomal aberrations, which were detected in two independent cases, were: t(1;20)(q12.3;p13), del(3)(p12) and del(1)(p13).

Table 1. Patients' characteristics

	No. of patients
Study period	10/88–10/91
Patients*	110
Male/female	58/52
Median age	63 (38–85) year
< 50	13
51–60	29
61–70	41
> 70	27
Diagnosis	
Multiple myeloma	104
Plasma cell leukaemia	6
Stage	
I	22
II	19
III	57
Unknown	6
Previous therapy	
No therapy	70
Chemo ± radiotherapy	33
Radiotherapy	5
Unknown	2
Type of monoclonal gammopathy	
Ig G	64
Ig A	24
Light chains	8
Non-secretory	10
Unknown	4
Total protein (g/l)	
≥ 100	25
< 100	82
Unknown	3
β_2-microglobulin (ng/l)	
≥ 4.0	24
< 4.0	30
Unknown or not done	56
No. of bone lesions	
0–1	45
> 1	61
Unknown	4
Bone marrow infiltration (%)†	
≤ 50	76
51–75	15
> 75	17
Unknown	2

* 2 patients were reported previously [9].
† Studied on cytological slides.

Sequential cytogenetic studies

15 patients were studied at diagnosis and at least once again in the course of disease (Table 2). In 4 patients karyotypes were normal at diagnosis and in remission. 5 of 8 patients with a

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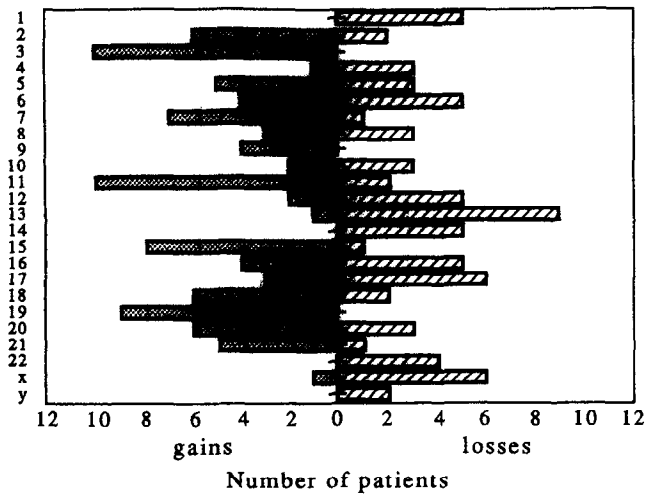

Fig. 1. Incidence of numerical chromosome abnormalities.

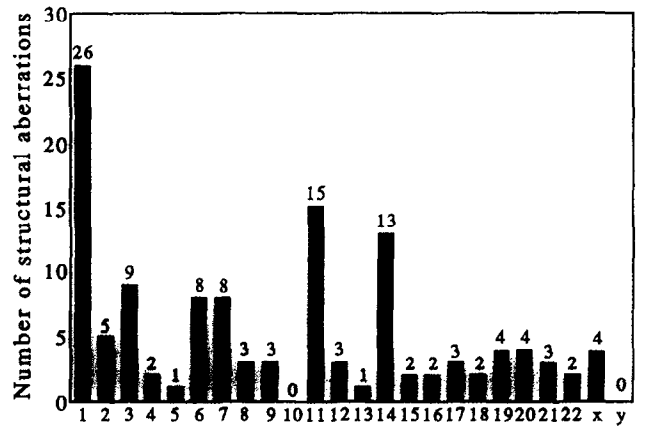

Fig. 2. Frequency and distribution of structural chromosome aberrations.

normal karyotype at diagnosis had an abnormal karyotype at disease progression. In 2 patients with an initial abnormal karyotype no remission was obtained and karyotypes remained abnormal. 1 patient with initial abnormal karyotype converted to normal in remission and reverted again at the time of progressive disease.

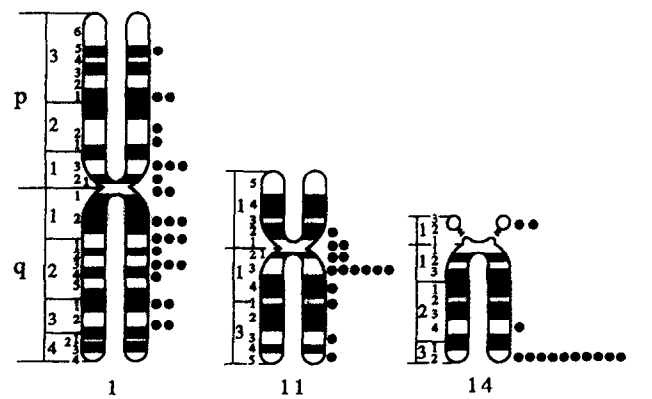

Fig. 3. Distribution of breakpoints in chromosomes number 1, 11 and 14. Each symbol represents the breakpoint of one structural cytogenetic defect.

Table 2. Results of sequential cytogenetic studies

Patient no.	Karyotype at diagnosis	Karyotype/status* at second analysis		Karyotype/status at third analysis	
1	46,XX	46,XX	Remission	Not done	—
2	46,XY	46,XY	Remission	Not done	—
3	46,XY	46,XY	Remission	46,XY	Remission
4	46,XY	46,XY	Remission	Not done	—
5	46,XY	Abnormal	PD	Abnormal	PD
6	46,XX	Abnormal	PD	Not done	—
7	46,XY	Abnormal	PD	Not done	—
8	46,XY	Abnormal	PD	Not done	—
9	46,XY	Abnormal	PD	Not done	—
10	46,XX	46,XX	PD	46,XX	PD
11	46,XX	46,XX	PD	Not done	—
12	46,XX	46,XX	PD	Not done	—
13	abnormal	46,XY	Remission	Abnormal	PD
14	abnormal	Abnormal	NC	Not done	—
15	abnormal	Abnormal	NC	Not done	—

* PD = progressive disease; NC = no change.

Concomitant cytogenetic/cytological studies

In 51 patients concomitant cytogenetic and cytological studies were performed. 39 of these had a normal, and 12 an abnormal karyotype. In the patients with normal karyotype 117 mitoses were studied. Only 10 of them originated from plasma cells, whereas 107 came from contaminating haematopoietic cells (not shown). In the patients with abnormal karyotype 27 mitoses were found. 20 of them were mitoses from plasma cells (not shown) and only 7 from other bone marrow cells ($P < 0.0001$).

Influence of clinical parameters on the chromosomal aberration rate

The clinical characteristics given in Table 1 were tested for their influence on the chromosomal aberration rate. Age, sex, concentration of total protein, type of monoclonal gammopathy, β_2-microglobulin level and number of bone lesions did not influence the aberration rate. On the other hand previous therapy, diagnosis, stage and percentage of bone marrow infiltration did so. An abnormal karyotype was most often found in pretreated patients, plasma cell leukaemia, stage III and notably in patients with more than 75% bone marrow infiltration (Table 3). In the multivariate analysis, only bone marrow infiltration

Table 3. Influence of clinical parameters on the chromosomal aberration rate

Clinical parameter	Aberration rate		*P*-value
Previous therapy			
No	16/70	(26%)	0.028
Yes	17/38	(39%)	
Diagnosis			
Multiple myeloma	28/104	(27%)	0.009
Plasma cell leukaemia	5/6	(83%)	
Stage			
I	1/22	(4%)	
II	4/19	(21%)	0.005
III	22/57	(39%)	
Bone marrow infiltration (%)			
< 50	11/76	(14%)	
51–75	7/15	(47%)	0.0000008
> 75	15/17	(88%)	

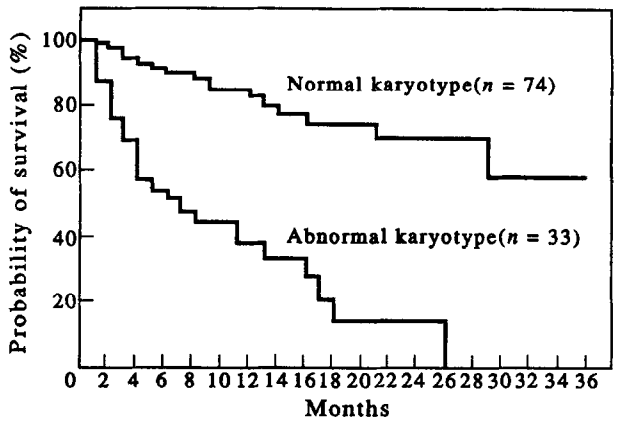

Fig. 4. Probability of survival of 107 patients from the time of cytogenetic analysis according to karyotype.

(more than 75% $P < 0.001$, 51–75% $P = 0.004$) and to a lesser extent stage III ($P = 0.012$) had an influence on karyotype.

Survival according to karyotype

Survival status is known for 107 of the 110 patients. From the time of cytogenetic analysis, projected median survival for the 33 patients with abnormal karyotype was 7 months, and for the 74 patients with normal karyotype it has not been reached after 36 months (Fig. 4). This difference was statistically significant ($P = 0.00001$). Projected 1 and 2 year survival is 86% and 72% for patients with normal karyotype and 38% and 15%, respectively, for patients with abnormal karyotype. In the multivariate analysis only abnormal karyotype ($P < 0.001$) and previous therapy ($P < 0.001$) remained of prognostic significance. Median survival of 10 patients with break point in chromosome 14q32 was comparable to the whole group with chromosomal aberrations (data not shown). Survival status is known for 68 of 70 patients who were untreated when cytogenetic analysis was performed. Projected median survival for 16 patients with pathological karyotype was 10 months, and for 52 patients with normal karyotype it has not been reached after 208 months (Fig. 5). The difference was again statistically significant ($P = 0.0017$). This unusually long lasting projected survival is only due to 1 patient with a disease duration of 208 months.

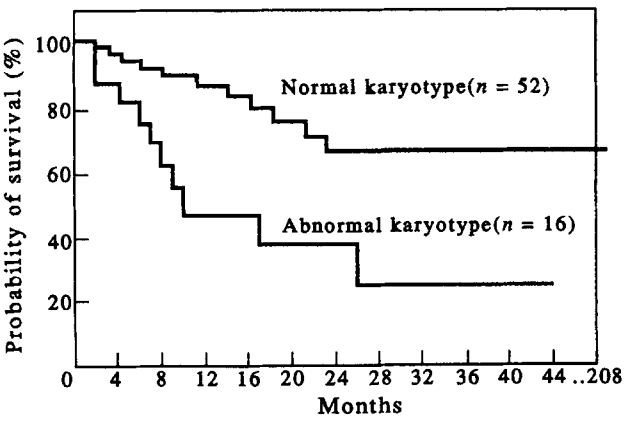

Fig. 5. Probability of survival of 68 untreated patients according to karyotype.

Probability of survival at 1 and 2 months is 87% and 67% for patients with normal karyotype and for patients with abnormal karyotype it is 48% and 38%, respectively. In the multivariate analysis, only abnormal karyotype was of prognostic significance ($P = 0.002$).

DISCUSSION

There are only a few published series of chromosome analyses in multiple myeloma [8]. Two investigations comprising 82 and 115 patients [4, 6], respectively, and several series with patient numbers between 4 and 36 [1–3, 5, 7, 17–21] have been reported. In our study of 110 patients the chromosomal aberration rate was relatively low and equalled 30%. In the above mentioned reports it varied between 20 and 64% with a median incidence of 30–40%. Although interleukin-6 is known to be a growth factor for myeloma cells [22, 23], our attempts to increase the anomaly rate by adding this growth promoting activity to the cultures were unsuccessful. This failure may be due to technical reasons. Possibly the interleukin-6 concentration used by us or the culture periods may have been inadequate. On the other hand there may have also been principal reasons for our inability to increase the anomaly rate by interleukin-6. Proliferation of contaminating normal haematopoietic cells may have been stimulated *in vitro*. Furthermore, a possible precursor of malignant plasma cells, the spotted cell, may be unresponsive to interleukin-6 [24].

Therefore, the reason for the low incidence of chromosomal anomalies in multiple myeloma may be due to the slow proliferation of plasma cells leading to few cytogenetically analysable mitoses. This assumption is confirmed by our concomitant cytogenetic–cytological studies. Analysis of 51 patients reported in detail elsewhere [25] confirms our previous findings [26] and is an indirect but strong evidence that in almost all patients with a normal karyotype mitoses did not originate from plasma cells but rather from other haematopoietic cells. If this assumption is true, the incidence of chromosomal abnormalities would rise considerably by using effective mitogens specific for plasma cells.

A 14q+ chromosome in 10 patients resulting from a t(11;14)(q13;q32) in 4 of them and from a t(8;14)(q24;q32) in 1 patient, was the most consistent chromosomal anomaly. This is in good accordance with findings of others [1–6, 8, 19, 20, 27–29]. We have recently described 2 patients with a t(1;20)(q12.3;p13) [9]. As reported by others [2, 4–6], chromosome 1 was most frequently involved in structural aberrations but without remarkable clustering of breakpoints. On the other hand, we observed no cases with a Philadelphia chromosome [18] or a 17p+ marker chromosome [17] and only few cases with 6q− and 7q− [8].

The incidence of chromosomal anomalies was clearly influenced by clinical parameters. It was highest in pretreated patients, patients with plasma cell leukaemia, stage III and dense bone marrow infiltration, which are all characteristics of advanced disease. We did not find correlations between clinical characteristics and specific chromosomal anomalies. Dewald *et al.* [4] found an increased rate of chromosomal anomalies in patients with advanced, active disease and plasma cell leukaemia. In the study of Liang *et al.* [1] advanced disease was again accompanied by a higher incidence of cytogenetic defects. Clark *et al.* [7] have studied the influence of pretreatment upon karyotype. They did not find a higher incidence of chromosomal anomalies in pretreated patients, but the type of anomalies was different compared with those without previous therapy. How

the degree of bone marrow infiltration affects the frequency of chromosomal aberrations has not been studied thus far.

Our sequential analyses in 15 patients confirm that the chromosomal aberration rate is largely influenced by disease activity. 5 of 8 patients with initial normal karyotype had converted to abnormal at disease progression. In 1 patient the initial abnormal karyotype normalised during remission and reverted again when disease advanced. Dewald *et al.* [4] studied 19 patients twice. In 3 cases the karyotype had changed, but the authors did not correlate alterations with clinical status.

In our study untreated as well as treated patients with abnormal karyotype had a significantly shorter survival than those with normal karyotype, confirming that karyotype is an independent prognostic factor in multiple myeloma. In smaller series comprising 25 and 32 patients, respectively [4, 7] the same findings were noted.

The aim of future cytogenetic research must lie in achieving higher proliferation rates of plasma cells *in vitro*. It may then be possible to study karyotypes of the malignant clone in the majority of cases. This will probably not be achieved by refined cytogenetic techniques but rather by using effective mitogens, as has been successfully shown in chronic lymphatic leukaemia [30], a disease comparable to multiple myeloma in some aspects. When we are able to obtain cytogenetic information of plasma cells in almost all patients, the significance of karyotype in multiple myeloma may be considerably clarified.

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