

Cytogenetic Data as a Prognostic Factor in Multiple Myeloma Patients: Involvement of 1p12 Region an Adverse Prognostic Factor

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Abstract. *Background:* Multiple myeloma (MM) is characterized by great clinical heterogeneity. Among known prognostic factors the cytogenetic abnormalities are thought to be of major importance. The aim of this study was to correlate certain chromosomal abnormalities with immunoglobulin isotype and survival in MM patients. *Patients and Methods:* Forty-nine Greek MM patients, homogeneously treated with conventional-dose chemotherapy, were cytogenetically studied by direct culture of bone marrow cells and G-banding technique. *Results:* Twenty-four patients had a normal karyotype while the remaining 25 patients presented numerical and structural abnormalities. Recurrent structural abnormalities were observed. Translocations involving the 14q32 region were observed in 8 cases, while 6 cases exhibited a *del(1)(p12)*. We confirmed the negative impact of chromosomal abnormalities on the overall survival of MM patients and we also showed that *t(11;14)* had a worse impact on disease outcome as compared to *t(14q32)* with an unidentified partner chromosome. The presence of *del(1)(p12)* significantly worsened the prognosis in MM patients. No correlations existed between the association of immunoglobulin isotype with survival or certain chromosomal changes. *Conclusion:* Further studies are indicated at the molecular level to clarify the exact role and the prognostic value of 1p12 involvement in MM patients.

Multiple myeloma (MM) is a clonal B-cell malignancy characterized by infiltration of bone marrow from malignant plasma cells producing a monoclonal immunoglobulin. Conventional cytogenetic studies have found abnormal karyotypes in 30-55% of MM patients (1-5), while studies using FISH techniques have identified numerical

chromosomal changes in at least 65-90% of patients (6,7). MM is characterized by a great clinical heterogeneity with survival ranging from a few months to more than 10 years. A median survival of about 2 years was obtained with conventional chemotherapy, but new high-dose therapy trials have improved the overall survival (8-11). Therefore, it is of major importance to recognize clinical or biological parameters predicting the disease outcome and possibly to identify subgroups of patients for whom intensive therapy could be indicated. Among known prognostic factors reported for MM patients, cytogenetic abnormalities are thought to be of major importance. Studies using conventional cytogenetics or FISH techniques showed that partial or complete deletions of chromosome 13 or translocations involving the 13q as well as hypodiploidy confer poor prognosis in MM (1,4,12-15). Translocations involving chromosome 14 at band q32, the immunoglobulin heavy chain (IgH) locus, are thought to be important for MM. The most common of these translocations is the *t(11;14)(q13;q32)*. A number of studies have referred to the prognostic influence of *t(14q32)* in MM patients (16-19). Also a correlation of *t(14q32)* type with immunoglobulin isotypes have been reported (16,20).

We report here cytogenetic data in Greek MM patients by conventional cytogenetics undertaken in our laboratory, detecting the frequency and the type of chromosomal abnormalities and correlating them with immunoglobulin isotype and survival.

Patients and Methods

Sixty-nine patients with MM were studied in our laboratory by conventional cytogenetics. We included in this study 49 patients successfully karyotyped, for whom the overall survival time was available. Of them 26 were male and 23 were female, aged 45-82. All the patients were treated with conventional-dose chemotherapy. A total of 38 patients were karyotyped at the time of diagnosis. Eleven patients had, prior to the cytogenetic study, received either 2-3 courses of conventional chemotherapy (9 patients) or local radiotherapy (2 patients). We considered that the prior therapy did not influence either the patients' survival or the

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Key Words: Multiple myeloma, conventional cytogenetics, chromosomal abnormalities, involvement of 1p12, prognosis.

Table I. Involvement of chromosome 1,3,11 and 14 in structural aberrations in Greek MM patients.

Case	Immunoglobulin type	Karyotype
1	IgD	48 ~ 51 < 2n + >, XY, del(1)(p12) , + del(3)(q12) , del(3)(p11) , +5, +6, +9, +10, -11, der(14)t(3;14)(q21;q32) , +15, +16, -20.
2	Light-chain-only	43 ~ 45 < 2n - >, XX, del(1)(p12) , del(3)(p11) , -7,-10, -11, -12.
3	IgG	44 ~ 45 < 2n - >, XY, -10, add(14)(q32) , -22.
4	IgG	40 ~ 45 < 2n - >, XX, + del(1)(p12) , -7, -8, -9, -11, -16, -20, + 4 m
5	Light-chain-only	48 ~ 50 < 2n + >, XX, + del(1)(p12) , der(2)t(2;8)(p25;q24) , -4, add(6)(q27) , +7, -8, +17,+19, add(14)(q32) , +2 m.
6	Light-chain-only	43 ~ 45 < 2n - >, XX, + del(1)(p12) , -5, del(6)(q25) , -8, -9, add(11)(p14) , -12, der(14)t(11;14)(q13;q32) , -16, + add(17)(p13) , -19, + m.
7	Light-chain-only	60 ~ 62, < 2n + >, XX, +X, + del(1)(q32) , + del(3)(q13) , -5, +6, +6, +8, +11, + der(11)del(11)(q23)add(11)(p13) , +16, +18, +18, + add(19)(p13) , +22, +4 m
8	IgD	47 ~ 50 < 2n + >, XX, del(1)(p12) , der(14)t(11;14)(q13;q32) , -17, +20, +2 m.
9	IgG	51 ~ 53 < 2n + >, XX, -1, der(2)t(2;11)(q3?;q13) , -3, +11, +18, +19, +19, +22, +2 m.
10	IgG	38 ~ 39, < 2n - >, X,-X, der(1)t(1;3)(p13;p13) , + del(3)(q12) , -4, der(5)t(3;5)(p13;p15) , del(7)(q22) , der(7)t(3;7)(q13;p12) , -8, der(8)t(3;8)(p13;p23) , -14, -14, -16, -17, der(19)t(3;19)(p13;q13) , -20, -21, -22, + 3 m.
11	IgG	50 ~ 52, < 2n + >, XY, add(3)(q29) X2 , der(14)t(11;14)(q13;q32) , + 5 m.
12	IgA	88 ~ 90, < 4n - >, XY, -1, -1, add(1)(p31) X2 , -2, add(2)(p24) X2 , -3, -3, del(3)(p12) , del(3)(q12) X2 , -4, -4, -6, -6, del(6)(q13)X2 , -7, -7, -8, -9, -9, -11, -11, -12, -14, -14, der(14)t(11;14)(q13;q32) X3 , -15, +17, -18, -19, +20, +11 m.
13	IgA	49 ~ 50 < 2n + >, XY, -1, del(1)(p21) , + del(3)(q13) , + der(3)del(3)(q13)add(3)(p25) , -8, der(8)t(1;8)(p21;p21)X2 , +9, -10, -11, add(15p) , + add(19)(q13) , + 1 m.
14	IgG	44 ~ 45 < 2n - >, X, -X, -1, dup(1)(q21q44) , add(9)(q34) , add(14)(q32)

cytogenetic findings. The monoclonal component was immunoglobulin G (IgG) in 25 patients, IgA in 11 patients, IgD in 4 patients, 8 patients expressed light chains only and 1 patient was nonsecretory MM. Chromosome preparations were made from bone marrow aspirates directly, without *in vitro* culture, by using the G-banding technique as described elsewhere(21). As many cells as possible were analysed in each case and no fewer than 20. An abnormal clone was defined as two or more metaphases with either the same structural anomaly or the same extra chromosome, or as three or more metaphases lacking the same chromosome. Karyotypes were described according to the International System of Human Cytogenetic Nomenclature (ISCN 1995) (22).

Statistical analysis. The effect of various parameters (ploidy level, type of monoclonal protein secreted and certain chromosomal abnormalities) on survival was assessed by the Kaplan-Meier method and groups were compared using the log-rank test. The influence of each variable was assessed using multivariate analysis (Cox's regression model). The relationships among various parameters were evaluated using Pearson's Chi-square test and Fisher's exact test. The results were considered statistically significant when $p \leq 0.05$. Statistical analysis was performed using the SPSS 11.0 software.

Results

Twenty-four patients (49%) had a normal karyotype, while the remaining 25 (51%) presented several numerical and/or structural chromosomal abnormalities.

Numerical abnormalities. Patients with abnormal cytogenetic analysis were classified into two groups depending on the observed modal chromosomal number, hypodiploid/hypotetraploid and hyperdiploid, in a manner similar to that reported by Smadja *et al.* (4) and Fassas *et al.* (13). Fifteen patients had a hyperdiploid karyotype, while 10 patients had a hypodiploid/hypotetraploid karyotype.

Structural abnormalities. The chromosomes most commonly involved in structural abnormalities were 1 (in 11 cases), 14 (in 8 cases), 3 (in 7 cases) and 11(in 6 cases) (Table I). Recurrent structural abnormalities were identified. Chromosome 1 was involved mainly as deletion of the short arm or it participated in translocations with other chromosomes. **Del(1)(p12)** was observed in 6 cases. Chromosome 3 was involved as **del(3q)** or **del(3p)** or it is participated in translocations with other chromosomes. **Del(3)(q12)** was observed in three cases, while **del(3)(q13)** and **del(3)(p11)** in two cases each. It is of note that, in a hypodiploid case with 38-39 chromosomes, translocations involving the 3p13 region with different partner chromosomes were observed. Chromosome 14 was involved in 8 cases as **add(14)(q32)**. In three of these cases the extra material was not recognized, while in the remaining cases there was a translocation **t(11;14)(q13;q32)** (in 4 cases) and

Table II. Chromosomal abnormalities in relation to immunoglobulin isotype in 49 Greek MM patients.

	IgG	IgA	IgD	Light chains only	Non-secretory	Total
Normal karyotype	13	7	1	2	1	24
Abnormal karyotype	12	4	3	6	-	25
Hyperdiploid karyotype	7	2	3	3	-	15
Hypodiploid karyotype	5	2	-	3	-	10
del(1)(p12)	1	-	2	3	-	6
add(14)(q32)	3	1	2	2	-	8

a t(3;14)(q21;q32) (in one case). Chromosome 11 participated in translocations with chromosome 14 in four cases, as described above, with chromosome 2 as t(2;11)(q3?;q13) in one case, while del(11q) and add(11p) were also observed. Three cases with del(1)(p12) and four cases with add(14)(q32) were hyperdiploid.

Presence of chromosomal abnormalities in relation to the immunoglobulin type. Thirteen among 25 IgG MM patients and 7 among 11 IgA MM patients presented a normal karyotype, while 3 among 4 IgD patients and 6 among 8 light-chain-only MM patients exhibited an abnormal karyotype. Among 15 patients with a hyperdiploid karyotype, 7 were IgG, 2 were IgA, 3 were IgD and 3 were light-chain-only MM. Among 10 hypodiploid/hypotetraploid patients, 5 were IgG, 2 were IgA and 3 were light-chain-only MM. Del(1)(p12) was observed in one IgG patient, in 2 IgD and in 3 light-chain-only MM patients. Add(14)(q32) was observed in 3 IgG patients, in one IgA, in 2 IgD and in 2 light-chain-only MM patients (Table II). No correlations existed between the various parameters (ploidy level, t(14q32), del(1)(p12) and the type of monoclonal proteins secreted).

Survival. The median overall survival in the 49 Greek MM patients studied was 16 months. The impact of karyotypic abnormalities on survival was considerable as the difference in median survival between patients with normal and abnormal karyotype (22 months *vs* 3 months, respectively) was statistically significant ($p=0.0002$) (Figure 1). The median survival in 15 cases with hyperdiploid karyotype was 6 months *vs* 3 months in 10 cases with hypodiploid/hypotetraploid

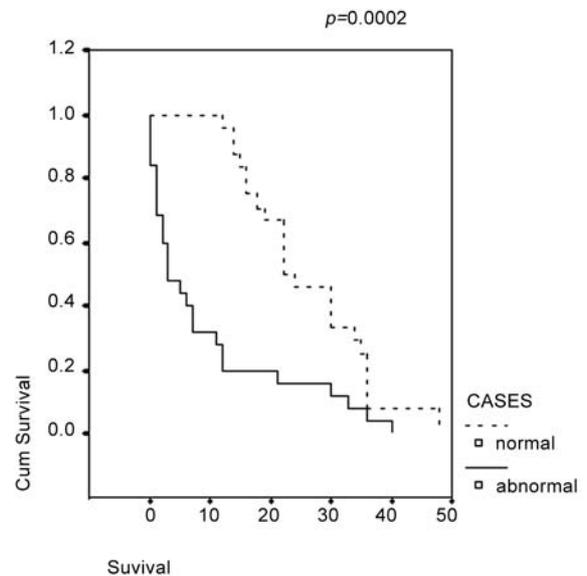


Figure 1. Overall survival in relation to chromosomal aberrations.

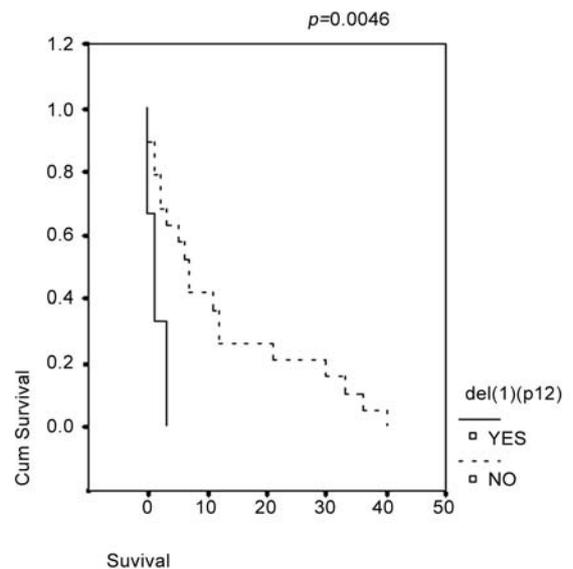


Figure 2. Overall survival in relation to del(1)(p12).

metaphases ($p=0.8472$). The median survival in 8 cases with add(14)(q32) was 2 months *vs* 7 months in 17 abnormal patients without this abnormality $p=0.1293$. On the other hand, among patients with add(14)(q32) a statistical significant difference in survival existed between the subgroups of t(11;14) and add(14)(q32) with an unknown partner chromosome (1 month *vs* 3 months, respectively, $p=0.0213$). Also, the presence of del(1)(p12) worsened significantly the prognosis. Thus, the median survival in 6 cases with del(1)(p12) was 1 month *vs* 7

months in 19 abnormal patients without this abnormality ($p=0.0046$) (Figure 2). Testing different combinations of the chromosomal aberrations $\text{add}(14)(q32)$ and $\text{del}(1)(p12)$, we found that survival between patients without $\text{add}(14)(q32)$ or $\text{del}(1)(p12)$ and patients with both $\text{add}(14)(q32)$ and $\text{del}(1)(p12)$ was significantly different (7 months vs 0 months, respectively, $p=0.0055$). Calculating the median overall survival for the 38 patients with chromosome studies at diagnosis (18 normal and 20 abnormal), we obtained similar results (median survival 15.5 months). The median overall survival for the 18 patients with a normal karyotype was 22 months vs 5 months in 20 patients with an abnormal karyotype, $p=0.0012$. Regarding the impact of monoclonal protein secreted on survival, no statistically significant influence was demonstrated concerning the total population and the subgroup of patients with abnormal karyotype. The multivariate analysis confirmed that, in the group of patients with abnormal karyotype, the only factor predicting the overall survival independently was $\text{del}(1)(p12)$ ($p=0.028$) and the relative risk was 4.43.

Discussion

Chromosomal abnormalities represent the main prognostic factor in several hematological malignancies, especially acute leukemias. Such a prognostic factor was less evident in MM patients by conventional cytogenetics, either because of difficulties in harvesting malignant cells or because of a low proliferative index, resulting in difficulties in obtaining clonal metaphases. Patients with an abnormal karyotype were reported to have a much greater chance of early death than patients with a normal karyotype (3,9,11). In this study, the negative impact of karyotypic abnormalities on survival of MM patients was well established.

Most published studies of MM patients using conventional cytogenetics have shown hypodiploidy in approximately 10-30%. A shorter survival and a poor response to chemotherapy have been proven for patients with hypodiploidy (1,3,4,13). In this study, hypodiploidy/hypotetraploidy was found in 10 patients, who had a shorter median survival (3 months) than patients with a hyperdiploid karyotype (6 months). However, a significant correlation between ploidy level and survival was not well defined.

A number of studies using conventional cytogenetics or FISH techniques have demonstrated the major prognostic value of chromosome 13 abnormalities, detected by these techniques in 15-20% and 40-50% of MM patients, respectively. Thus MM patients with complete or partial loss of chromosome 13 or translocations of 13q present a poor survival, whatever the treatment strategies (5,12,13,15,23). In our study, chromosome 13 abnormalities were not defined. In two cases loss of chromosome 13 was found, but only in two metaphases each. Thus the lack of numerical aberrations of chromosome 13 in this study might be explained by the

probability that more analyzed metaphases would be needed. On the other hand, involvement of chromosome 13 in unidentified marker chromosomes could not be excluded.

Translocations involving the chromosome 14 at band q32, the immunoglobulin heavy chain (IgH) locus, is a frequent finding in MM. The most common of these translocations are the $t(11;14)(q13;q32)$ and the $t(4;14)(p16;q32)$ detected in MM patients by FISH techniques in approximately 15-20% and 10-12%, respectively (16,19). The detection of $t(11;14)(q13;q32)$ in MM patients by conventional cytogenetics or interphase FISH has been reported to be associated with an unfavorable outcome and clinical features suggestive of aggressiveness (5,23). However, in a large study using FISH techniques, it was shown that patients with the $t(11;14)$ had no worse survival as compared with patients without this abnormality (7). Also, in another study, the prognostic value of specific translocations involving the 14q32 region was evaluated (18). Among them $t(11;14)$ was demonstrated to be a predictor of a long survival at least with the use of intensive chemotherapy strategies, while $t(4;14)$ was shown to predict a short survival and a poor response to chemotherapy. However, the significance of translocations $t(14q32)$ with an unidentified chromosomal partner still remains obscure. In this study, we found 8 patients with $\text{add}(14)(q32)$. In 4 of them this abnormality was recognized as $t(11;14)(q13;q32)$, in another as $t(3;14)(q21;q32)$, while in the 3 remaining cases the extra material on the 14q32 region was not identified. Patients with $\text{add}(14)(q32)$ had a shorter median survival (2 months) when compared with patients without this abnormality (7 months), but this difference in survival was not statistically significant. On the other hand, among patients with $\text{add}(14)(q32)$ a statistically significant difference in survival existed between the subgroups of $t(11;14)$ and $t(14q32)$ with an unidentified partner chromosome (1 month vs 3 months, respectively, $p=0.0213$).

Abnormalities involving the long arm of chromosome 1 are a frequent finding in MM and they have been associated with disease progression (24,25). In our study, chromosome 1 was involved in 11 cases, while $\text{del}(1)(p12)$ was detected in 6 cases. It is of note that, in cases 4,5,6 (Table I), in addition to $\text{del}(1)(p12)$, two normal chromosome 1 were present. On the other hand, in the cases with $\text{del}(1)(p12)$, involvement of the 1p12 region in unidentified marker chromosomes or in hidden unbalanced translocations could not be excluded. Whatever the case, the presence of 1p12 involvement worsened significantly the prognosis. To our knowledge, there are no literature data concerning the prognostic value of involvement of the 1p12 region in MM patients. Interestingly, 4 among 6 cases with $\text{del}(1)(p12)$ also shared involvement of 14q32 region. However, the multivariate analysis confirmed that, in the group of patients with abnormal karyotype, the only negative factor predicting the overall survival independently was $\text{del}(1)(p12)$ ($p=0.028$) and the relative risk was 4.43.

Comparing chromosomal abnormalities seen in MM patients at diagnosis (38 cases) with abnormalities observed after diagnosis (11 cases), we did not find any valuable difference suggesting an association of certain aberrations with disease evolution.

Concerning the presence of chromosomal abnormalities in relation to the immunoglobulin type, in our study IgG MM patients seemed to have the same opportunity for normal or abnormal karyotype. On the other hand, 7 among 11 IgA MM patients had a normal karyotype, while 3 among 4 IgD and 6 among 8 light-chain-only MM patients exhibited an abnormal karyotype. Previous studies showed an association between certain chromosomal abnormalities and the immunoglobulin isotype. Thus, a strong association between t(4;14) and the IgA isotype as well as a correlation between t(11;14) and light-chain-only MM has been shown (16,19). In another study (20), a very high incidence of t(11;14) in IgM, IgE and non-secretory MM was reported, but not in IgD, in which the t(11;14) has the same incidence (2 out of 9 cases) as that of IgG and IgA MM. In our study, 2 among 4 IgD MM had an add(14)(q32), which was recognized as t(3;14)(q21;q32) in one case and as t(11;14)(q13;q32) in the other.

In conclusion, by analyzing our results of 49 Greek MM patients homogeneously treated with conventional-dose chemotherapy, we confirmed the negative impact on survival of karyotypic abnormalities. Though the number of cases studied was not large, we showed that t(11;14) had a worse impact on disease outcome as compared with t(14q32) with an unidentified partner chromosome. Also, it was shown that involvement of the 1p12 region represents an adverse prognostic factor for MM patients. Further studies are indicated at molecular level to clarify the exact role and the prognostic value of 1p12 involvement in MM patients.

Acknowledgements

The technical assistance of Mrs Athanasia Babanaraki is gratefully acknowledged.

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Received April 15, 2004

Revised August 9, 2004

Accepted August 20, 2004