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Conventional Cytogenetics and FISH [del13q, del17p, t(11;14), t(4;14)] Findings and Their Relationship with Other Risk Factors in Multiple Myeloma

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ABSTRACT

Multiple myeloma (MM) represents a malignant proliferation of plasma cells in bone marrow. The prognosis is highly variable and markedly affected by a number of prognostic features. We aimed to determine the relationship between conventional cytogenetics and FISH [del13q, del17p, t(11;14), t(4;14)] findings and other prognostic factors in MM. In our study, we investigated the frequencies and the types of cytogenetic abnormalities in 50 MM patients. The most common chromosomal abnormality was hypodiploidy observed in 40.5% of 42 patients (17/42) screened with conventional cytogenetic analysis. Del 13q was detected in 37.5% of 48 patients (18/48)) screened with fluorescence in situ hybridization (FISH). 29 patients were investigated for del 17p, t(11;14), and t(4;14). Del 17p was detected in 3 (10.3%), t(11;14) in 7 (24.1%), t(4;14) in one (3.4%) of them. "International Staging System" (ISS) stage was increased as the "Durie-Salmon" (DS) stage increased. We didn't find a relationship between the cytogenetic abnormalities that we studied and DS or ISS stages.

Keywords: Multiple myeloma, Cytogenetics, Molecular biology, Prognosis

ÖZET

Multipl Myelomda Konvansiyonel Sitogenetik ve FISH [del13q, del17p, t(11;14), t(4;14)] Bulguları ve Diğer Risk Faktörleri ile İlişkisi

Multipl miyelom (MM) malign plazma hücrelerinin kemik iliğinde çoğalması ile karakterize bir hastalıktır. Hastalık benzer klinik tablolara yol açsa da prognoz oldukça değişkendir. MM'da konvansiyonel sitogenetik ve FISH [del13q, del17p, t(11;14), t(4;14)] bulguları ile diğer prognostik faktörler arasındaki ilişkinin saptanmasını amaçlandı. Çalışmamızda 50 MM olgusunda sitogenetik anormalliklerin sıklığı ve tiplerini araştırdık. Konvansiyonel sitogenetik ile değerlendirilen 42 olguda en sık saptanan anormallik %40.5 (17/42) oran ile hipodiploidi oldu. Fluorescence in situ hybridization (FISH) ile del 13q araştırılan 48 olgunun 18'inde (%37.5) del 13q saptandı. Del 17p, t(11;14), t(4;14) araştırılan 29 olgunun 3'ünde (%10.3) del 17p; 7'sinde (%24.1) t(11;14); 1'inde (%3.4) t(4;14); saptandı. "Durie-Salmon" (DS) evre arttıkça "International Staging System" (ISS) evrenin de arttığı görüldü. Değerlendirilen sitogenetik özelliklerin DS ve ISS evre ile ilişkisi bulunmamıştır.

Anahtar Kelimeler: Multipl myelom, Sitogenetik, Moleküler biyoloji, Prognoz

INTRODUCTION

Several prognostic factors have been identified in MM including age, low performance status, serum levels of lactate dehydrogenase (LDH), C-reactive protein (CRP), beta-2 microglobulin (ß2-M), syndecan-1 (CD138), CD 56, CD 45, CD 87, and soluble interleukin-6 receptor (sIL-6R), bone marrow plasma cell labeling index (PCLI), bone marrow microvessel density (MVD), DS stage, and ISS stage.[1-17] As the management of myeloma patients has shifted to more intensive treatment strategies and these prognostic factors have become inefficient to determine the best treatment protocoles for patients, new prognostic factors became needed in order to guide therapy and to identify the patients who might have benefits from more aggresive chemotherapy regimens. In recent years, several studies have confirmed that cytogenetic abnormalities are of prognostic significance in MM, as in acute leukemias and solid malignancies.[18-22] Conventional cytogenetics and FISH analysis contribute to diagnosis of MM, evaluating the treatment protocoles, and determining the prognosis. As MM is a malignancy of terminally differentiated B cells with low proliferative activity, it is difficult to detect the cytogenetic abnormalities in myeloma patients. Abnormal cytogenetics are found in only 30-50% of patients. Typically, previously treated or relapsed patients have a higher frequency of chromosome abnormalities than the ones with newly diagnosed disease, reflecting an increased proliferative activity of myeloma cells in advanced stage disease. FISH is a relatively new cytogenetic technique utilizing labeled DNA probes to analyze the cellular or chromosomal DNA or RNA in a sample. Hyperdiploid karyotype is found in approximately 65% of patients. Pseudodiploidy and hypodiploidy are found in 15% and 20% of patients, respectively. Most commonly reported abnormalities are detected at chromosomes 3, 5, 7, 9, 11, 15, and 19.[23] Chromosome 14q32, carrying immunoglobulin heavy chain (IgH) region, plays an important role in pathogenesis of MM. In myeloma patients, translocations of t(11;14), t(4;14), t(14;16), t(6;14), t(8;14) can be detected with FISH analysis.[23-28] Del 13q14, del 17p, and hypodiploidy are found to be associated with poor prognosis.[29,30] Recently published studies have revealed that chromosome 1q21 copy number gain is a poor prognostic factor. It has been postulated that chromosome 1q21 has a significant impact on pathogenesis of MM and may be the target cytogenetic abnormality in treatment.[31,32] In our study, we performed the cytogenetic analysis of myeloma patients admitted to our clinic, in addition to their clinical and biochemical evaluations. We aimed to determine the types and the frequencies of cytogenetic abnormalities and their relationships with other prognostic factors.

MATERIALS and METHODS

Patients: We studied 50 MM patients diagnosed and treated at hematology department. We didn't use any exclusion criteria in patient selection. Thirty-one of the patients were men (62%) and 19 of the patients were women (38%). Median age was 64 years (range 35-78). Clinical and laboratory characteristics including age, sex, hemoglobin concentration, white blood cell and platelet counts, serum levels of calcium (Ca), creatinine (Cr), albumin, LDH, B2-M, CRP, immunoglobulin classes and concentrations of serum and urinary monoclonal protein components, percentage of plasma cells in bone marrow, DS, modified renal DS, and ISS stages were registered at the time of the diagnosis in all patients. 17 of patients (34%) were given first step conventional chemotherapy while 33 of patients (66%) were not.

Method: The cytogenetic analysis of bone marrow samples were performed in two different centers because of the variety of social security foundations of the patients. Cytogenetic evaluations of 32 patients (64%) were performed in the first center and of 18 patients (36%) in the second. Bone marrow samples of all patients were taken into vacutainer tubes containing standart dose lithium heparin (85 IU). Forty-two of the samples were analyzed with conventional cytogenetics. The presence of del 13q was investigated in 48 patients with FISH analysis. In 29 patients t(4;14), t(11;14), and del 17p were also investigated in addition to del 13q with FISH. At the first center bone marrow cells were cultured with lymphocytes for 48 hours. FISH analysis were performed by using RB probe for del 13q, IgH/CCND1 DC/CF for t(11;14), IGH/FGFR DC/DF for t(4;14), and p53 for del 17p. At least 100 cells were counted for each probe. At the second center bone marrow cells were cultured with lymphocytes for 72 hours and 200 cells were counted at least. Del 13q was investigated with FISH by using LSI D13S319(13q14.3) Spectrum

Orange (Vysis) or 13q14 Specific Probe Direct Green (Q-Biogene) probes. All samples were drawn after obtaining formal written consent from the patients, and the research was carried out in accordance with the Helsinki Declaration.

Statistical Analysis: Statistical analysis was performed by Statistical Package for Social Sciences (SPSS) 11.5 software (SPSS Inc., Chicago, IL, United States). Whether the continuous variables were normally distributed or not were determined by using Shapiro Wilk test. Continuous variables were expressed as mean ± standard deviation or median (minimum - maximum), where applicable. Qualitative data were presented as number of patients and (%). Whereas, the difference between normal and abnormal groups regarding for normally distributed data were evaluated by using Student's t test, otherwise, Mann Whitney U test was applied. Nominal data were analyzed by Chi-square or Fisher's Exact test, where appropriate. A p value less than 0.05 was considered statistically significant.

RESULTS

A total of 50 patients, 31 men and 19 women, were included in the study. Median age was 64 years (range 35-78). All of the patients were grouped according to Durie-Salmon (DS) staging system. There were 14 patients (28%) with stage 1, 12 patients (24%) with stage 2, and 24 patients (48%) with stage 3. Staging according to modified renal DS staging system revealed stage A in 37 patients (74%), stage B in 13 patients (26%). Staging according to ISS revealed stage 1 in 19 patients (38%), stage 2 in 9 patients (18%), stage 3 in 22 patients (44%). Patient's sexualities, DS, modified renal DS and ISS stages are listed in Table 1. Seventeen of patients (34%) were given first step conventional chemotherapy while 33 of patients (66%) were not.

Table 1. Patient's sexualities, ages, "Durie-Salmon" Stages, "Modified Renal Durie-Salmon" Stages and "International Staging System" stages

Sexuality	**Number (n)**	**%**
Female	**19**	**38%**
Male	31	62%
Total	50	
Age	Median: 64 (range 35-78)	
Durie-Salmon Stage		
1	14	28%
2	12	24%
3	24	48%
Modified Renal DS‡ Stage		
A	37	74%
B	13	26%
ISS* Stage		
1	19	38%
2	9	18%
3	22	44%

Abbreviations: ‡; "Durie-Salmon", *; "International Staging System"

Forty-two patients (84%) were evaluated with conventional cytogenetics. Seventeen (40.5%) of 42 patients had hypodiploidy, 1 (2.3%) had tetraploidy, 3 (7.1%) had near tetraploidy, 2 (4.7%) had hyperdiploidy, and 7 (16%) had other chromosomal abnormalities including del 13q, complex karyotype, chtb(7)(q10), -22, -Y, del(17)(p13), del(3)(q25), each observed in one patient (chtb: chromatide break). Data obtained with conventional cytogenetic analysis are summarized in Table 2.

Del 13q was observed in 18 (37.5%) of 48 patients evaluated with FISH. Del 17p, t(11;14), and t(4;14) were investigated in 29 of the 48 patients. Del 17p

Table 2. Results of 42 patients who were evaluated with conventional cytogenetic analysis

Cytogenetic abnormalities (n=42)	Number	Percentage
Hypodiploidy	17	40.5%
Tetraploidy	1	2.30%
Near Tetraploidy	3	7.10%
Hyperdiploidy	2	4.70%
Other chromosomal abnormalities‡	7	16%

Abbreviations: ‡: "del 13q (n=1), komplex caryotype (n=1), chtb†(7)(q10)) (n=1), -22(n=1), -y (n=1), del(17)(p13)(n=1), del(3)(q25) (n=1)"

†: chromatide break

Table 3. FISH Results of patients who were evaluated for del 13q, del 17p, t(11,14), t(4,14)

FISH Results	Patients (n)	Percentage
del 13q (+)	18 (18/48)	37.50%
del 17p (+)	3 (3/29)	10.30%
t(11,14)(+)	7 (7/29)	24.10%
t(4,14) (+)	1 (1/29)	3.40%
Other abnormalities‡	3 (3/29)	10.30%

Abbreviations: ‡ trisomy 11, trisomy 17, amplification of CCND1(Cell cycle regulatory proto-oncogene/cyclin D1)

Table 4. The relationship between DS stage and modified renal DS stage.

DS‡ Stage	Modified renal DS‡ Stage		Total	p
	Stage A	Stage B		
Stage 1	14	-	14	
Stage 2	11	1	12	p<0.001
Stage 3	12	12	24	
Total	37	13	50	

Abbreviations: ‡; "Durie-Salmon"

was found in 3 (10.3%), t(11;14) in 7 (24.1%), and t(4;14) in 1 (3.4%) of them. Trisomy 11 was found in one patient, trisomy 17 in another patient, and amplification of CCND1 (Cell cycle regulatory proto-oncogene/cyclin D1) in 2 patients. Cytogenetic data obtained with FISH analysis are summarized in Table 3.

There were no statistically significant differences regarding the DS stages with the types of serum M proteins and light chains in urine (p>0.05).

A statistically significant correlation was found between DS stage and DS renal stage (p<0.001) (Table 4). There weren't any statistically significant associations between DS stages and data obtained from conventional cytogenetic analysis or FISH (p>0.05). There were no statistically significant differences regarding the ISS stages and the types of serum M proteins and light chains in urine (p>0.05).

DS and renal DS stages were found to be significantly correlated with ISS stages (p<0.001 and p=0.002, respectively) (Table 5,6). There wasn't a statistically significant association between ISS stage and data obtained from conventional cytogenetic analysis and FISH (p>0.05). No significant association between prior chemotherapy and cytogenetic abnormalities became apparent (p>0.05). A statistically significant correlation was found between DS stage and DS renal stage with B2-M level (p<0.001, p<0.001, respectively). We didn't find any associations between cytogenetic abnormalities with advanced age, sex, hemoglobin concentration, white blood cell and platelet counts, serum levels of Ca, Cr, albumin, LDH, B2-M, CRP, immunoglobulin classes and concentrations of serum and urinary monoclonal protein components, percentage of plasma cells in bone marrow, DS, modified renal DS, and ISS stages (p>0.05).

DISCUSSION

Patients with MM have widely variable clinical courses. Prognostic classification of myeloma patients is very important for evaluation of different treatment protocols and prognosis. In recent years, it has been shown that there is a strong correlation between the presence of cytogenetic abnormalities and prognosis.[18-22]

Typically, previously treated or relapsed patients have a higher frequency of chromosomal abnormalities than the ones with newly diagnosed disease, suggesting that the proliferative activity of myeloma cells increases in advanced stage disease. In our study, regarding the cytogenetic abnormalities, we didnt't find a significant difference between patients who had chemotherapy and those who didn't. This may be due to the small number of patients included in our study.

Hyperdiploid karyotype is found in approximately 65% of myeloma patients. Pseudodiploidy is observed in 15% and hypodiploidy is observed in 20% of the patients. The most common abnormalities are observed at chromosomes 3, 5, 7, 9, 11, 15, and 19.23 In our study, hypodiploidy was the most common chromosomal abnormality detected by conventional cytogenetic analysis (40.5%). Abnormalities at chromosomes 3, 7, 13, 17, and 22 were also observed.

Tablo 5. The relationship between DS stage and ISS stage.

DS‡ Stage	ISS* Stage			Total	p
	Stage 1	Stage 2	Stage 3		
Stage 1	11	3	0	14	<0.001
Stage 2	4	5	3	12	<0.001
Stage 3	4	1	19	24	<0.001
Total	19	9	22	50	

Abbreviations: ‡; "Durie-Salmon", *; "International Staging System"

Tablo 6. The relationship between ISS stage and modified renal DS stage

ISS* Stage	Modified renal DS‡ stage		Total	p
	Stage A	Stage B		
Stage 1	18	1	19	0.002
Stage 2	8	1	9	0.002
Stage 3	11	11	22	0.002
Total	37	13	50	

Abbreviations: ‡; "Durie-Salmon", *; "International Staging System"

In a study of 155 patients with newly diagnosed myeloma, cytogenetic abnormalities were found in 39% of the patients. Partial or complete deletions of chromosome 13 or 11q abnormalities were found to be associated with poor prognosis and co-existance of both of these chromosomal abnormalities were strongly correlated with shortened survival. In this study, it was shown that advanced age, elevated B2-M levels, and IgA isotype were associated with unfavourable karyotype.[33] In a study of Facon et al. chromosome 13 abnormalities detected by FISH analysis were found to be strongly related with poor prognosis, especially in combination with a serum B2-M level of higher than 2.5 mg/L.[34] Furthermore, detection of deletion/monosomy of chromosome 13, t(4;14), t(4;16), and del 17p13 were found to be related with poor prognosis.[35,36] In our study, we didn't find an association between the chromosomal abnormalities detected by conventional cytogenetic analysis and serum levels of B2-M, advanced age, and IgA isotype. In a study, 89 newly diagnosed myeloma patients were screened by FISH analysis to detect deletions of 13q, 17p, and 11q and the presence of t(11;14). Del 13q was observed in 44 patients (44.9%), del 17p was observed in 22 patients (24.7%), 11q abnormalities were observed in 14 patients (15.7%), and t(11;14) was observed in 7 patients. All these chromosomal abnormalities were found to be significantly correlated with poor prognosis.[37] t(11;14) is one of the most common translocations in MM, resulting in cyclin-D1 (cyclin D1/CCND1) upregulation. Cyclin D1 plays an important role in starting the G1 phase of the cell cycle. t(11;14) is strongly related with cyclin D1 overexpression. Cyclin D1 overexpression may also be seen in MM in the absence of t(11;14) supporting that there may be other mechanisms of cyclin D1 deregulation.[38] In our study, we detected cyclin D1 overexpression by FISH in two patients. Zojer et al. detected del 13q by FISH analysis in 48 of 104 (46.2%) newly diagnosed MM patients. In this study, it was observed that patients with del 13q were more likely to have stage 3 disease, higher serum levels of B2-M, and higher percentage of bone marrow plasma cells. They also found that myeloma cell proliferation (Ki-67) was markedly increased in patients with del 13q and del 13q was associated with lower rate of response to conventional-dose chemotherapy. It was shown that del 13q was correlated with increased proliferative activity representing an independent poor prognostic factor in MM.[39]

We didn't find any associations between cytogenetic abnormalities and advanced age, hemoglobin concentration, serum levels of Ca, LDH, and CRP, DS stage, DS renal stage, and ISS stage but we found that eleveted B2-M levels were significantly related with DS, DS renal, and ISS stages suggesting cytogenetic abnormalities in MM to be independent prognostic factors. Detection of del 13q with del 17p and t(11;14) was increased by FISH suggesting that FISH analysis is important in determining the prognosis of MM. Two patients died after a short time from the diagnosis; one died after 147 days and the other died after 16 days from the diagnosis. Both of them had del 13q by FISH; one of them also had complex karyotype abnormality, suggesting that complex karyotype abnormalities and del 13q by FISH are associated with unfavourable prognosis. Recent studies

revealed that abnormalities of chromosome 1, especially 1q21 copy number gain, are poor prognostic parameters.[31,32] It is suggested that chromosome 1q21 has a significant impact on pathogenesis of MM and may be the target cytogenetic abnormality in treatment strategies. In our study, we found loss of chromosome 1 in one patient who had complex karyotype abnormalities and also high percentage of del 13q. In FISH analysis, we didn't use a probe for chromosome 1q21, so we can't make a speculation about the frequency of 1q abnormalities but we plan to investigate the prognostic impact of copy number gain at chromosome 1q21 in our further studies.

In conclusion, the most common abnormality was hypodiploidy detected in 40.5% of 42 patients analysed with conventional cytogenetics. Del 13q was observed 37.5% percent of 48 patients analysed with FISH for detection of del 13q. We didn't find a relationship between the cytogenetic abnormalities that we studied and DS, DS renal, or ISS stages.

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