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ΕΡΕΥΝΗΤΙΚΗ ΕΡΓΑΣΙΑ

Cytogenetic findings in 126 patients with multiple myeloma
A retrospective single-centre study

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ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2023, 40(3):349–355

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OBJECTIVE **To analyze the relationship between cytogenetic abnormalities, prognosis, and stage of multiple myeloma (MM) patients at diagnosis.** METHOD **The medical records of 126 patients diagnosed with MM between January 1st, 2013 and December 31st, 2020 were retrospectively reviewed. Most patients were assessed using conventional cytogenetics (CC) and some with interphase fluorescence *in situ* hybridization (I-FISH).** RESULTS **A total of 126 adult patients meeting the International Myeloma Working Group diagnostic criteria of MM were identified. Out of these patients, 64 (51%) were male and 62 (49%) female (1.03:1 ratio) with a mean age of 62.2 years. The patients' median overall duration of survival after diagnosis was 32 months. CC was performed on 113 (90%) patients, with abnormal karyotypes being found in 18 (16%). On the whole, 31 patients had FISH analysis, 22 (71%) of which had a normal result, and in 9 (29%) deletion on chromosome 17 was found.** CONCLUSIONS **Our patients presented with advanced disease with frequent complications, primarily because of the infiltration of plasmatic cells. The study demonstrated that, even though the CC analysis and FISH are performed on non-enriched plasma cells, they still have informative value. Moreover, they are essential for risk stratification in MM patients at diagnosis.**

Κυτταρογενετικά ευρήματα σε 126 ασθενείς με πολλαπλό μυέλωμα – μια αναδρομική μελέτη ενός κέντρου

Περίληψη στο τέλος του άρθρου

Key words

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Multiple myeloma (MM) is a rare B-cell neoplasm characterized by the accumulation of plasma cells in the bone marrow. Other clinical manifestations of MM include hypercalcemia, anemia, and renal dysfunction caused by the excessive production of monoclonal immunoglobulin protein (M protein).

MM is the second most common hematologic cancer, accounting for 1% of neoplastic diseases, with an incidence of 4.5–6 per 100,000 per year. The median age of onset is 69 years, with men showing a slightly higher prevalence compared to women. The survival duration ranges from a few months to more than 10 years.[1] There has been an increased incidence in the past few decades primarily because of the improved diagnostic techniques. Some studies have shown several risk factors associated with MM, like obesity, occupational exposure to pesticides, organic solvents, and radiation.[2]

MM is characterized by several numerical and structural aberrations, abnormal karyotypes, translocations, and copy number changes. The abnormalities found in patients with MM are primary and secondary, and are included in risk-stratification systems. Primary cytogenetic abnormalities (CA) are trisomies of odd-numbered chromosomes or translocations, usually involving the immunoglobulin heavy chain (IgH) gene locus on chromosome 14 and a partner chromosome.[3] The partner chromosomes that are most commonly found are chromosomes 4, 6, 11, 14, and 20.[4] Primary translocations are associated with a hypodiploid karyotype (up to 44–45 chromosomes), and they usually occur in the early premalignant stages of MM.[5] Translocations that are associated with poor prognosis are t(4;14), t(14;16) and t(14;20).[6–8] As a standard risk are considered patients with trisomies or translocation t(11;14).[9] Primary trisomies usually involve odd-numbered chromosomes 5,

7, 9, 11, 13, 15, and they lead to hyperdiploid karyotype (more than 46, but less than 76 chromosomes).[10] The most common secondary chromosomal aberrations in MM patients are monosomy or deletion of chromosome 13 (del 13q), deletion (del 17p) or monosomy of chromosome 17, amplification or duplication of chromosome 1.[10,11] The abnormal karyotypes reported in patients with MM are usually between 20% to 40%.[7,12,13]

The early-stage or premalignant condition which always preceded MM is called monoclonal gammopathy of undetermined significance (MGUS).[14] Over time, the disorder may slowly progress and evolve into aggressive plasma cell leukemia.

The most common risk-stratification system is the International Staging System (ISS), based on two parameters, serum beta-2 microglobulin and albumin, and patients are divided into three groups.[15]

To overcome the limitations of ISS, the Revised ISS (R-ISS) was proposed by the International Myeloma Working Group (IMWG) in 2015 to predict the prognosis of the disorder.[1,16,17] The system includes chromosomal aberrations, serum lactate dehydrogenase levels, and serum albumin and beta-2 microglobulin levels.

MATERIAL AND METHOD

The medical records of 126 patients diagnosed with MM between January 1st, 2013, and December 31st, 2020 were retrospectively reviewed. The study was conducted at the University Hospital Sveta Marina, Varna, Bulgaria, approved by Medical University "Prof. Paraskev Stoyanov", Varna, Bulgaria (ethics no 103/27.5.2021). It was conducted in accordance with the Declaration of Helsinki ethical principles and good clinical practices.

Criteria to include patients were as follows: patients at the age of 18 or older, patients with MM diagnosed according to IMWG criteria, patients with either conventional cytogenetic or interphase fluorescence *in situ* hybridization (I-FISH) analysis. Patients that don't fulfil these criteria were excluded. The following variables were studied at diagnosis in each patient: age, sex, bone marrow plasma cell infiltration, type of MMISS stage, and karyotypes.

Our study investigated the relationship between cytogenetic abnormalities, prognosis, and stage of MM patients at diagnosis. Most patients were assessed by conventional cytogenetics (CC) and some with I-FISH. Conventional karyotyping was performed on short-term cultured bone marrow (BM) aspirate samples following the standard cytogenetic method, and chromosomes were stained using GTG banding with trypsin and Giemsa stain.[18,19] When no abnormality was found, the karyotype study was considered sufficient when a minimum of 20 metaphases were available for review. When a clonal abnormality was found, a minimum of 10 metaphases were analyzed.[19] I-FISH was performed according to laboratory-validated protocols using commercially developed probes.[18] I-FISH analysis included probes for either TP53 deletion probe for the detection of abnormal copy numbers of chromosome 17 and the deletion of chromosome 17 – del(17p), dual-colour break apart rearrangement probe for immunoglobulin heavy chain (IGH) on chromosome 14q32 and translocation/dual fusion probes for t(4;14), t(14;16). At least 200 interphase cells were analyzed for each probe.

The karyotypes were classified as normal, with a single anomaly, and with complex karyotypes based on the International System for Human Cytogenomic Nomenclature (ISCN).[20] According to ISCN, a complex karyotype is defined as ≥3 chromosome abnormalities. An abnormal clone is identified when two or more metaphases show the same structural abnormality. Our laboratory performed conventional karyotyping (CK) and I-FISH analysis on each BM sample.

Statistical analysis

Statistical comparisons were made by the Contingence Chi-square test. The Kaplan-Meier method was used to determine the median overall survival from diagnosis to death. A $p<0.05$ was considerated to denote statistical significance. All statistical analyses were performed using GraphPad Prism 8 (GraphPad Software, LLC).

RESULTS

A total of 126 adult patients meeting the IMWG diagnostic criteria of MM were identified. Out of these patients, 64 (51%) were male and 62 (49%) female (1.03:1 ratio). The mean age of diagnosis was, respectively, 62.5 and 62.8 years. The demographic outline is shown in table 1. At the time of diagnosis, 66 (52%) patients were at ISS stage III, 30 (24%) at ISS stage I, and 30 (24%) at ISS stage II. Most of the patients (49.39%) had IgG type of MM, 21 (17%) had IgA, and 27 (21%) had light chain MM.

Conventional karyotyping was performed on 113 (90%) of 126 patients, 17 (15%) who also had I-FISH analysis. The other 13 (10%) of 126 were analyzed with I-FISH only. On the whole, 30 patients had I-FISH analysis. Karyotyping was successfully performed on 96 (85%) out of 113, and 17 (15%) had no metaphase growth for chromosome analysis. Normal karyotype was found in 77 (68%) out of 113 patients. Abnormal karyotypes were found in 18 (16%) – 11(61%) of them had complex karyotypes, and 7 had karyotypes with a single anomaly (39%) (tab. 2). Statistical significance is established between patients at different ISS stages and the result from CA. Most of them with abnormal karyotypes were in ISS III (n=15) and 4 in ISS II. All of the patients in ISS I have normal karyotype (p=0.0369).

On the whole, 31 patients had I-FISH analysis, 22 (71%)

Table 1. Characteristics of 126 patients with multiple myeloma (MM).

	Characteristic or follow-up data		Total (%) n= 126 (100%)
	Sex		
	Male n= 64 (51%)	Female n= 62 (49%)	
Age groups			
<50	9 (14%)	5 (8%)	14 (11%)
50–64	29 (45%)	24 (39%)	53 (42%)
65–74	18 (28%)	20 (32%)	38 (30%)
≥75	8 (13%)	13 (21%)	21 (17%)
Age of diagnosis			
(y), mean	62.5	62.8	62.2
Type of MM			
IgA	12 (19%)	9 (15%)	21 (17%)
IgG	23 (36%)	26 (42%)	49 (39%)
Light chain	17 (27%)	10 (16%)	27 (21%)
Other	12 (19%)	17 (27%)	29 (23%)
ISS stage			
ISS I	19 (30%)	11 (18%)	30 (24%)
ISS II	10 (16%)	20 (32%)	30 (24%)
ISS III	35 (55%)	31 (50%)	66 (52%)

ISS: International Staging System

of them had normal results, and in 9 (29%) of them, deletion on chromosome 17 –del(17p)– was found. Conventional cytogenetic and I-FISH analyses were performed on 17 patients (15%). In three cases, the karyotype was normal but had abnormal I-FISH results–del(17p). In one patient with complex karyotype, the I-FISH result was normal, and in one patient with complex karyotype, the I-FISH result showed deletion on chromosome 17 – del(17p) (tab. 3).

All 126 patients had a bone marrow evaluation as well. We found statistical significance between patients with normal and abnormal karyotypes and the percentage of plasma cells in bone marrow (p=0.002). In 42 (55%) out of 77 patients with normal karyotype, bone marrow plasma cell infiltration was more than 30%, in 32 (42%), it was less than 30%, and in 3 (3%) the aspirate was insufficient for analysis. In all 11 patients with complex karyotypes, bone marrow plasma cell infiltration was >30%. In 6 out of 7 patients with a single anomaly in the karyotype, bone marrow plasma cell percentage was found to be over 30% (p=0.002).

The median overall duration of survival (OS) of the patients after diagnosis was 32 months. For the patients younger than 70 years, the duration of survival was 34 months and 16 months for patients older than 70 years (p=0.04). The median overall survival between male and

Table 2. Cases with abnormal karyotypes.

Complex karyotypes
46,XX,-1,-1,-C(?8),-C,i(10)(q10),+11,del(12)(p12),add(14)(q32),del(Dq),del(20)(q11),+4~5mar{cp15}
46,XX,-1,-C(?12),+?der(11),t(1;11)(q21;q23),-D,+18,+F(20)[8]/46,XX[2]
45,XY,t(11;14)(q?13;q32),-D(?13),-D(?14),+mar[9]/46,XY[1]
55~56,XY,del(1)(p13),+1,+3,+5,+6,+del(6)(q21),+9,+i(?9)(q10),+10,+14,+19,+mar{cp8}/46,XY[12]
59,XX,+3,+B,+B,+C,+C,+C,+D,+F,+F,+G,+3mar[2]/46,XX[18]
53~60,XY,del(1)(p12),+2,+3,+5,+9,+C,+18,+19,+20,+21,+22,+2~3mar{cp3}/46,XY[9]
44,X,-Y,+der(1),t(1;11)(q31;q12),-4,add(7)(q?36),-7,del(8)(p21),-?13,+mar[5]/46,XY[15]
79~88,XY,-1,+2,+add(3q),+add(Bq),+add(Bq),+add(Cq),+C,+C,+C,+C(10?),+C(12),+add(Dq), +add(Dq),+D,+D,+inv(16)(pq),+del(16)(q?),+17,+18, +19,+19,+20,+20,+21,+21,+22,+22,+mar(3) {cp10}
57~62,XY,+2,+3,+4,+5,+7,+C,+C,del(11)(q?22),+D,+16,+17,+18,+19,+20,+21,+3mar{cp11}/46,XY[9]
47,XY,+1,del(8)(q23),-8,t(11;14)(q13;q32),del(22)(q13),+22[2]/46,XY[18]
45~46,XY,-2,-C,-C,del(11)(q22),add(Dq),+3mar[10]/46,XY[3]
Karyotypes with single anomaly
46,XY,del(16)(q21)[5]/46,XY[15]
45,X,-Y[6]/46,XY[14]
45,X,-Y[14]/46,XY[6]
46,XX,del(13)(q14)[15]/46,XX[5]
46,XX,del(21)(q22)[6] /46,XX[19]
47,XX,del(5)(q?15-q33),+21 [20]
45,XX,-11[2]/46,XX,-11,+16[13]/46,XX[5]

Table 3. Cases with I-FISH analysis.

Normal karyotype	Abnormal I-FISH result
46,XX[20]	TP53/17cen
46,XX[20]	TP53/17cen
46,XY[20]	TP53/17cen
Complex karyotype	**Normal I-FISH result**
47,XY,+1,del(8)(q23),-8,t(11;14)(q13;q32),del(22)(q13),+22[2]/46,XY[18]	
Complex karyotype	**Abnormal I-FISH result**
45~46,XY,-2,-C,-C,del(11)(q22),add(Dq),+3mar[10]/46,XY[3]	TP53/17cen

I-FISH: Interphase fluorescence *in situ* hybridization

female patients was 41 and 28 months, respectively (p=0.5) (fig. 1).

The median duration of survival between patients with normal and abnormal results from the conventional cytogenetic analysis showed statistical significance (p=0.03) (fig. 2). Survival from diagnosis was significantly longer in patients at ISS I stage and significantly shorter in patients at the ISS III stage (p=0.008) (fig. 3).

No statistical significance regarding OS was found in patients with del(17p) and normal result from I-FISH analysis (p=0.68).

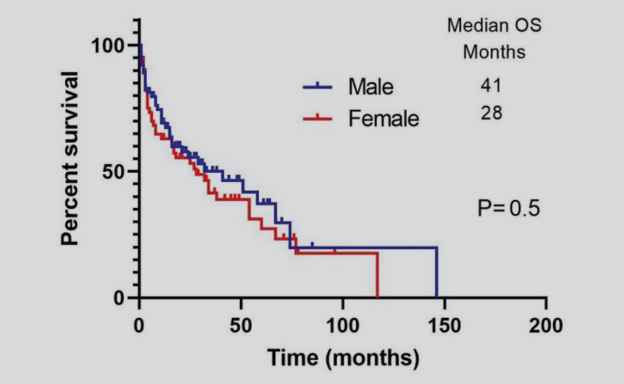

Figure 1. Kaplan-Meier curves demonstrating (OS) from diagnosis between male and female patients with multiple myeloma.

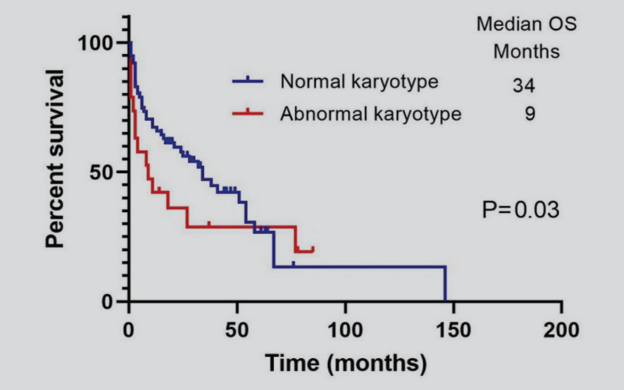

Figure 2. Kaplan-Meier curves demonstrating overall duration of survival (OS) from diagnosis based on the result from conventional cytogenetic analysis.

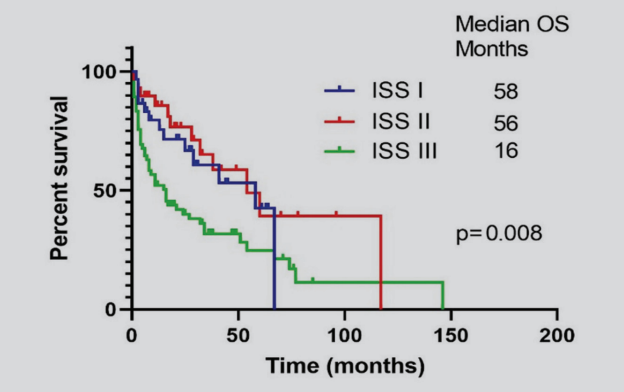

Figure 3. Kaplan-Meier curves demonstrating overall duration of survival (OS) from diagnosis based on the International Staging System (ISS) stage.

DISCUSSION

MM is a heterogeneous disease characterized by complex genetic background, including chromosomal aberrations, translocation– 90% of which involve chromosome 14, and copy number changes. Patients typically have complex karyotypes with recurrent numerical and structural abnormalities.

MM usually is observed in patients over the age of 60. The ages of patients included in our study group ranged from 38–91 years, and most of the patients are presented in the 5th and 6th decade of life, with a mean age of 62 years. Men are affected more frequently than women. Our patients, in general, were presented with advanced disease with frequent complications primarily because of the infiltration of plasmatic cells.

Some of the risk-stratification systems use CA to predict the outcomes of the disorder. Standard risk is associated with patients with trisomies and translocation t(11;14).[21,22] In terms of poor prognosis, del(17p), t(4;14), t(14;16), and t(14;20) are considered to be the most informative CA regardless of treatment, and they are associated with poor overall survival.[10,23,24] Poor outcome is also associated with the presence of del(13q) or monosomy 13 detected with

conventional karyotyping.[9,10,23] The simultaneous presence of del(1p) in patients with t(4;14) and del(6q) in patients with del(17p) increases the risk compared with the presence of a single anomaly.[25] Usually, t(11;14) is associated with a good prognosis, but if there is also del(1p) in the karyotype, this can worsen the risk.[26]

In our study, CA was successful in 85% of the patients, which is within the reported in the literature rate (30–92%).[7,27,28] The detection of cytogenetic aberrations in patients with MM is limited due to the low proliferative index of myeloma cells.[29,30] Despite that, the detection of abnormal metaphases can predict adverse prognosis. It has been reported that in 50–70% of all cases the karyotype is normal.[31–33] In our study, 68% of the patients have shown normal karyotypes. Abnormal karyotypes were described in 14–56% of cases in previous studies;[7,30,34] while our results show aberrations in 16% of the patients. I-FISH abnormalities were found in 29% of our patients, compared with 36–86% of the reported.[35–38] They all had P53 deletion, which is linked with poor prognosis.[16,23,39,40] I-FISH analysis dramatically improved the detection rate; however, it is often difficult to detect abnormalities in patients with low levels of plasma cells.[12,30] This can be enhanced with the use of immunomagnetic bead enrichment of plasma cells.[41] IMWG has been established as the gold standard I-FISH analysis performed on CD138-positive cells.[17,41]

We acknowledge the limitations in our study, especially the unavailability to use that kind of enrichment of plasma cells from bone marrow samples. Moreover, the enrichment of myeloma cells with immunomagnetic beads in combination with flow cytometry is reportedly able to increase the detection rate and monitor minimal residual disease and relapse in patients with MM.[41]

In conclusion, our study demonstrated that even though the conventional cytogenetic analysis and I-FISH are performed on non-enriched plasma cells, they still have informative value. Moreover, they are essential for risk stratification in MM patients at diagnosis. They can be used to detect the progression of the disease or when there is no response to the treatment.

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ΠΕΡΙΛΗΨΗ

Κυτταρογενετικά ευρήματα σε 126 ασθενείς με πολλαπλό μυέλωμα – μια αναδρομική μελέτη ενός κέντρου

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ΣΚΟΠΟΣ Η ανάλυση της σχέσης μεταξύ κυτταρογενετικών ανωμαλιών, της πρόγνωσης και του σταδίου των ασθενών με πολλαπλό μυέλωμα (ΠΜ) στη διάγνωση. **ΜΕΘΟΔΟΣ** Αναλύθηκαν αναδρομικά οι ιατρικοί φάκελοι 126 ασθενών με ΠΜ που διαγνώστηκαν κατά το χρονικό διάστημα μεταξύ 1ης Ιανουαρίου 2013 και 31ης Δεκεμβρίου 2020. Οι περισσότεροι εκτιμήθηκαν με συνήθη κυτταρογενετική ανάλυση (ΚΑ) και αρκετοί με I-FISH. **ΑΠΟΤΕΛΕΣΜΑΤΑ** Και οι 126 πληρούσαν τα διαγνωστικά κριτήρια του ΠΜ της International Myeloma Working Group. Από αυτούς τους ασθενείς 64 (51%) ήταν άνδρες και 62 (49%) γυναίκες (σχέση 1,03:1), με μέση ηλικία τα 62,2 έτη. Η συνολική μέση διάρκεια επιβίωσης μετά τη διάγνωση ήταν 32 μήνες. ΚΑ διενεργήθηκε σε 113 (90%) ασθενείς και παθολογικός καρυότυπος βρέθηκε σε 18 (16%). Από το σύνολο, 31 ασθενείς υποβλήθηκαν σε ανάλυση FISH, και 22 (71%) από αυτούς εμφάνισαν φυσιολογικό αποτέλεσμα, ενώ από τους εν λόγω ασθενείς σε 9 (29%) βρέθηκε διαγραφή στο χρωμόσωμα 17. **ΣΥΜΠΕΡΑΣΜΑΤΑ** Οι ασθενείς της παρούσας μελέτης είχαν προχωρημένη νόσο με συχνές επιπλοκές κυρίως λόγω της πλασματοκυτταρικής διήθησης. Η μελέτη καταδεικνύει ότι η ανάλυση CC και το FISH που πραγματοποιούνται σε μη εμπλουτισμένα πλασματοκύτταρα εξακολουθούν να έχουν κάποια πληροφοριακή αξία. Επί πλέον, είναι απαραίτητα για τη διαστρωμάτωση του κινδύνου σε ασθενείς με ΠΜ κατά τη διάγνωση.

Λέξεις ευρετηρίου: Επιβίωση, I-FISH, Κυτταρογενετική ανάλυση, Πλασματοκύτταρα, Πολλαπλό μυέλωμα

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