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Cytogenetic abnormalities correlate with clinico-biological characteristics in 30 Moroccan multiple myeloma patients

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ABSTRACT

Background: The nonrandom recurrence of chromosomal abnormalities in multiple myeloma (MM) raises the possibility that they play a role in the pathophysiology and development of the disease. Fluorescence in situ hybridization (FISH) can identify a high frequency of certain abnormalities without the need for the proliferative and infiltrative index of malignant plasma cells required for conventional cytogenetic analysis. In this study, we describe the association between clinico-biological characteristics and chromosomal abnormalities in 30 Moroccan patients.

Methods: The analysis of cytogenetic data, conventional and molecular, of 30 cases of MM, obtained from our previously cytogenetic study, and correlation of the results with the clinico-biological data of these patients.

Results: The bone marrow of 5 of 21 patients (23 %) contained a chromosomally abnormal clone, and all karyotypes were complicated (>3 abnormalities). Interphase FISH (iFISH) has detected aberrations in 14 out of 30 (46 %) of the total cases. The proportion of plasma cells in the bone marrow was higher in patients with chromosomal abnormalities (median 29 %) ($p = 0.01917$) than in patients without abnormalities (median 11 %). Although there was a difference in the median ß-2 microglobulin percentage (13.8 % versus 6.8 %), it was not statistically significant ($p = 0.6818$). We also, categorized patients into those with a complex clone and those with a sole abnormality. Patients with high bone marrow plasma cell rate (median 45 %) and high rate of ß-2 microglobulin (median 24 %) showed a complex karyotype and a higher iFISH detection rate than those with plasma cells count for (median 20 %) and ß-2 microglobulin count for (median 11 %) but without statistical significance ($p = 0.4338$ *et* $p = 0.45$ respectively). Furthermore, patients with aberrations had significantly shorter overall survival (100 % for 800 days versus 150 days only).

Conclusion: Our research has shown that different subgroups of patients with MM can be classified based on the underlying genetic abnormalities. Chromosomal abnormalities (CA) may give the plasma cell a proliferative advantage, increasing the virulence of the disease and affecting overall survival.

1. Introduction

Multiple myeloma (MM) is a cancer that develops when a single clone of diotypic B lymphocytes and plasma cells proliferate in the bone marrow and create monoclonal immunoglobulins that are either full or incomplete. 10% of all hematological cancers and 1% of all neoplasms are related to MM [1,2].

The International Scoring System (ISS), a model staging approach for patients with MM, based on β2-microglobulin and albumin, allows the classification of newly diagnosed patients into three risk groups: high risk, intermediate risk and standard risk.

Cytogenetic analysis by interphase FISH (iFISH) is an important prognostic tool endorsed by the European Myeloma Network and the International Myeloma Working Group and the European Myeloma Network for MM diagnosis in all patients [3,4].

The diagnosis and risk stratification of MM are based on clinico-

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biological finding and cytogenetic tests to better define a patient's risk at diagnosis [5].

The presence of abnormal monoclonal plasma cells in the bone marrow, the presence of M protein in the serum or urine, and specific indicators of end-organ damage such as hypercalcemia, renal failure, anemia and bone lesions (CRAB) are used to make the diagnosis [4].

Variations in the underlying genetic make-up of myeloma cells contribute to the diverse clinical presentation of MM patients. These are the predictive indicators most commonly used to assess how biologically aggressive the disease is [6].

Myeloma is a disease characterised by chromosomal instability. Cytogenetic abnormalities (CA) have an impact on prognosis, for example in several hematological malignancies, especially acute leukaemias, as well as in myeloma. Currently it is being used to make medical decision for therapy [7].

A highly proliferative clone is more likely to have an aberrant karyotype, according to studies investigating the clinico-biological effects of CA in myeloma. This suggests that the likelihood that standard cytogenetic tests will find an aberrant clone in a myeloma patient is consistently correlated with the severity of the disease. In addition, a number of studies suggest that the underlying genetic and cytogenetic abnormalities are likely to be related to the observed clinical heterogeneity among myeloma patients [8].

Conventional cytogenetic tests show that only a third of people with MM have an abnormal karyotype [5]. They are often hampered by the low plasma cells proliferation as well as the limited extent of bone marrow involvement, as well as some chromosomal changes may be cytogenetically silent (cryptic abnormalities) [9].

The currently accepted method for analysing CA is iFISH. It shows abnormalities in about 90 % of MM patients. Due to the often-low number of plasma cells in diagnostic samples, it requires prior sorting but has the advantage of being independent of the mitotic index of the plasma cells [5].

The minimal requirement is the assessment of del(17p) (cytogenetic location of the *P53* gene) and t(4;14) involving the *IGH-MMSET / FGFR3* at diagnosis, but analyzing gains in 1q, del(1p), t(14;16) and t(14;20) are also recommended [3].

Our study aimed to describe the correlation between the CA and the clinico-biological, features of 30 Moroccan patients.

2. Patients and methods

2.1. Patient characteristics

This is a retrospective study preformed over a period of 13 months, from May 2017 to June 2018, of 30 MM newly diagnosed Moroccan patients, hospitalized at Cheikh Khalifa Hospital, and referred to the National Reference Laboratory of Mohammed VI University Of Health and Sciences (UM6SS), for conventional cytogenetic and fluorescence in situ hybridization (FISH) analysis.

Patients were included in the study if they met all of the International Myeloma Working Group (IMWG) criteria for defining MM (myeloma-defining CRAB features, abnormal monoclonal plasma cells in the bone marrow, and M protein in serum or urine) and if their individual clinico-biological characteristics were available.

Cytogenetic data were gathered from the results of our cytogenetic study performed previously [10].

Clinico-biological data were collected from the medical records of patients fulfilling the inclusion criteria. These data relate to the following parameters: Bone marrow plasma cells, Lytic bone lesions, Hypercalcemia, Serum M component, Light chain type, Hemoglobin, Creatinine and Albumin.

Written informed consents were also obtained from all the patients included. The cohort of patients included 16 men and 14 women.

2.2. Correlation with clinico-biological features and standard prognostic parameters

In order to understand the relationship between chromosomal abnormalities and clinico-biological manifestations, we classified MM patients in groups.

- 30 patients were classified into 2 groups: 14 cases with chromosomal abnormalities and 16 patients without.
- The heterogeneity observed in the results of conventional cytogenetic and iFISH allowed us to classify the patients with cytogenetic abnormalities into 2 subgroups.
  - The first subgroup contains 5 patients with complex karyotypes and two or more aberrations highlighted by iFISH using the recommended panel of probes.
  - The second subgroup consists of 9 patients who displayed chromosomal abnormalities using iFISH while the karyotype was normal or not done.

This classification prompted us to think about comparing the biological characteristics of these two subgroups, and correlating their cytogenetic profiles with other prognostic factors.

2.3. Statistical analysis

The statistical package R version 3.6.3 was used for the statistical analysis. The chi-square and Fisher exact tests were used to analyze nominal variables. The correlation between the variables was examined using the Spearman rank. The Kaplan-Meier technique was used to calculate survival curves.

A *p*-value less than 0.05 was regarded as statistically significant.

2.4. Overall survival follow-Up

The time between the date of diagnosis and the date of death from any cause or the last follow-up appointment was called overall survival (OS).

3. Results

3.1. Distribution of age and sex

The median age was 65 years, with 37 % in the 60–70 age group and a male predominance (Fig. 1).

3.2. Clinico-biological features

Below, Table 1 shows the biological and prognostic data of all analysed MM patients.

3.3. Conventional cytogenetic analysis results

Of the 30 patients, 21 has benefit from the conventional cytogenetic analysis, while 8 did not, and 1 patient cultured failed to grow.

Among the 30 MM, 21 patients had a hematologic karyotype of which only 5 (23 % of cases) had an abnormal clone with complex karyotypes (> 3 abnormalities).

There were: 2 cases of hyperdiploid group and 3 cases of non hyperdiploid group of which there are 2 hypodiploid and 1 hypotetraploid karyotype.

These identified cytogenetic abnormalities mainly concerned chromosomes 1, 11, 9 and 14 (Table 2).

The abnormalities involving the *IGH* locus located on chromosome 14q32 were found in 2 patients, including the translocation t (11;14) (q13; q32) which involves the *IGH* and *CCND* loci (*IGH/CCND*). The 1p34 deletion was identified in 2 patients (Table 2).

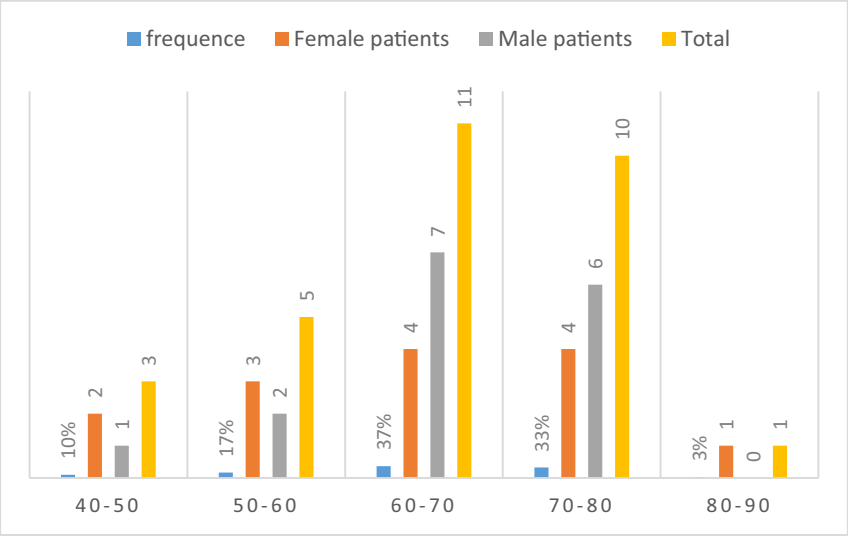

Fig. 1. Age and Sex distribution in the 30 MM studied cases.

Table1
Main clinico-biological characteristics of 30 MM patients.

Variable	All ($n = 30$)
Median age, years (range)	65 (41–81)
Sex, male/female,%	53/47
Bone marrow plasma cells,	
>25 %	7
<25 %	23
Lytic bone lesions,%	
present	13
absent	17
Hypercalcemia,%,	
(>1 mg/dL) higher than the upper limit of normal	6
Serum M component,	
Present, 1 or more g/dL	20
Absent	10
Light chain type,%	
k	16
L	13
Unknown	2
Hemoglobin, g/L	
>10 g/dl	14
<10 g/dl	16
Creatinine, mg/L	
>20 mg/L	12
<20 mg/L	18
Albumine g/l	
>35 g/L	18
<35 g/L	12
B_2-microglobulin, mg/L	
>2 mg/L	17
<2 mg/L	1
unknown	12
ISS%	
I	9
II	2
III	11
Unknown	8

3.4. iFISH analysis results

A total of 14 out of 30 (46 %) MMs cases displayed at least one recurrent abnormality by iFISH analysis. Table 2 provides a summary of findings.

The 17p13 deletion (cytogenetic location of the *P53* gene) and the duplication (1) (q21) involving the *CKS1B* gene were the most recurrent abnormalities with a frequency of 17 % each.

While the 14q32 / *IGH* translocation with an unknown partner was found in 4 cases (13 %), and the translocation t (4;14) translocation involving the *IGH-MMSET / FGFR3* gene in 2 cases (7 %).

3.5. Correlation between karyotype and iFISH

36 % (6/16) of normal MM karyotypes showed chromosomal abnormalities according to iFISH results. Furthermore, it highlighted two or more abnormalities in all the complex karyotypes.

3.5.1. Correlation between clinico-biological and cytogenetic features of patients with and without cytogenetic abnormalities

We analysed correlations between standard clinico-biological parameters including, bone marrow plasma cells, serum monoclonal protein, hemoglobin, serum calcium, albumine, ß-2 microglobulin and presence or absence of chromosomal abnormalities (Table 3).

There was a significant discrepancy between these 2 groups in the percentage of plasma cells in the bone marrow (median 29 %) ($p = 0.01917$) (Fig. 2).

Patients with ß-2 microglobulin counts (median 13.8 %) showed a higher FISH detection rate than those with ß-2 microglobulin count (median 6.8 %) but this difference is not statisticaly significant ($p = 0.6818$).

None of the other biological factors examined above were associated with the presence of cytogenetic abnormalities (Table 3).

3.5.2. Correlation between clinico-biological and cytogenetic features of patients with complexes and non-complexes abnormalities

The subgroup of 5 patients with complex chromosomal abnormalities had a higher percentage of bone marrow plasma cell rate (median 45 %) ($p = 0.01917$) than the subgroup of 9 patients with a single abnormality (median 20 %).

The percentage of ß-2 microglobulin was also higher in the first subgroup (median 24 %) compared to the second group (median 11 %), but this difference is not statistically significant ($p = 0.4338$ et $p = 0.45$, respectively) (Table 4).

3.6. Correlation between cytogenetic results and overall survival of MM patients

Patients with cytogenetic abnormalities had a median overall survival (OS) of 26 months (780 days), while patients without abnormalities had a median OS of 31 months (930 days). Kaplan-Meier curves

Table 2
FISH results abnormalities of 14 MM patients with a complex and normal conventional karyotype.

patient number	% Plasma cells befor cell sorting	% Plasma cells after cell sorting	FISH result	Conventional karyotype result
F/ 68	22 %	92	- IGH remanie - Del 17p - Del 1q	44,XX,der(1)t(1;21)(q11;q11),del(2)(p11;p25),t(3;14)(p21;q32),del(4)(q13),t(8;?;1)(q24.2;?;p32),−14,−22[19]/46,XX[9]
F/ 53	3 %	65	- IGH remanie - Del 17p	45–46,X,-X,der(1)del(1p34),+der(1)del(1)(q21),t(11;14) (q23;q32),−15,−16,−17,+mar1,+mar2[*cp*7]/46,XX[13]
F/ 68	15 %	82	- t(4;14) - Del 17p - Amp1q	82–87,XX,−4,−5,+del(6)(q13q23),+del(7)(q22q34),del(8)(q12q23),−10,t(11;14)(q13;q32),der(13)t(13;?)(p10;?),−13,−15,-17 × 2,−18,−20,der(21;?)(p12;?),-22 × 2,+mar1 × 3,+mar2 × 2,+mar3 × 2,+mar4[*cp*6]/46,XX[9]
M/ 63	24 %	95	- t(4;14)	49–50,XY,der(3)t(3;?)(P22;?),del(3)(p21),+del(6)(q16q23),+7,−8,+9,del(9)(q12q22),−11,add(13)(p11),+add(15)(p11),+21[*cp*4]/ 46,XY[14]
M/ 61	29 %	93	- Amp 1q - Del 1p	51,XY,+der(1)del(p34p13),+der(2)t(2;?)(p25;?),+5,+9,der(12)t(12;?)(p13;?), del(16)(p12),+18,der(20)t(20;?)(p13;?)[3]/46,XY[22]
F/ 56	1 %		- Del IGH	46,XX
M/ 68	12 %	80	- IGH remanie	46,XY
F/ 60	1 %	58	IGH remanie	46,XY
F/ 57	24 %	62	Amp 1q	46,XX
M/ 64	2 %	83	Amp 1q	ND
M/ 62	28 %	51	Amp 1q	ND
M/ 57	2 %	60	Del17p	46,XY
F/ 70	1 %	67	Del 17p	ND
F/ 75	1 %	70	Poliploidy	46,XX

Del 17p: Deletion 17p Amp 1q: Amplification 1q t(4;14): translocation (4;14) ND: not done.

Table 3
Correlation of various clinico-biological characteristics of MM patients with and without cytogenetic abnormalities.

Variable	Finding, median (range) without cytogenetic abnormalities ($n = 16$)	with cytogenetic abnormalities ($n = 14$)	P-val
Bone marrow PCs%	11 (4–45)	29 (4–81)	0.01917
Serum monoclonal protein (g/dL)	26 (5.3–47.8)	40 (27.9–52.1)	1
Hemoglobin (g/L)	11.2 (6.5–16.4)	10.3 (7.4–14.1)	0.5072
Calcemia (mg/L)	93 (84–105)	102 (71–134)	0.306
Albumine (g/L)	37 (18.8–47)	35.4 (21–44)	0.6524
ß-2 microglobulin (mg/L)	6.8 (1.78–37.06)	13.8 (2.46–39.5)	0.6818
Overal survival (OS) (Months)	31	26	

(Fig. 3) revealed an association between OS and the presence of cytogenetic abnormalities.

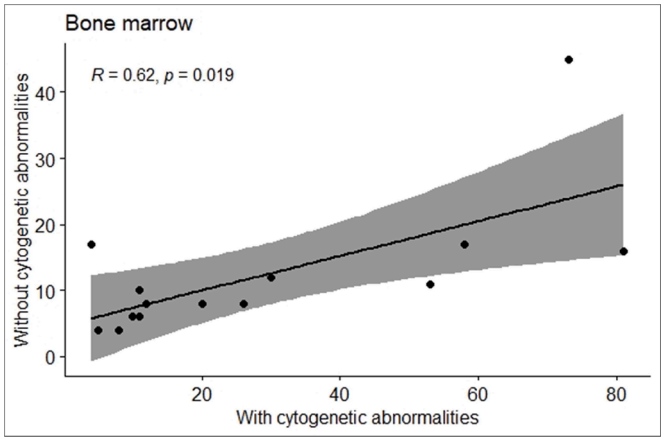

Fig. 2. bone marrow plasma cell (BMPC) percentage among patients with cytogenetic abnormalities and those without cytogenetic abnormalities.

Table 4
Correlation of clinico-biological data from patients with complex and non-complex cytogenetic abnormalities.

Variable	Finding, median (range) Patients with complex karyotype, and FISH abnormalities ($n = 5$)	Patients with normal karyotype/no karyotype and FISH abnormalities ($n = 9$)	P-val
Bone marrow PCs %	45 (10–73)	20 (4–81)	0.4338
Serum monoclonal protein (g/dL)	37 (23–52)	21 (10–27)	1
Hemoglobin (g/L)	8.4 (7.4–9.5)	11.55 (8.5–14.1)	0.2333
Calcemia (mg/L)	116.6 (94–134)	93.4 (71–107)	1
Albumine (g/L)	30 (21–36)	38 (28–44)	0.1333
ß-2 microglobulin ((mg/L)	24.1 (8.7–39.5)	11 (2.4–16.8)	0.45
1 FISH abnormality%	20	89	1
More than 1 FISH abnormality%	80	11	1

The probability of OS of patients without cytogenetic abnormalities (red) is 100 % for 800 days (26,6 months), and then drops to 90 % thereafter. However, the probability of OS with cytogenetic abnormalities (blue) drops to 90 % after only 150 days (5 months). However, the survival rates of the two groups are not statistically different. This is due to the small cohort.

4. Discussion

The clinical characteristics and progression of multiple myeloma are significantly influenced by cytogenetic alterations. Therefore, one of the most important prognostic variables is the detection of chromosomal abnormalities in malignant plasma cells [5].

Due to the limited proliferative activity of plasma cells, chromosomal abnormalities can be detected by standard karyotyping in only 18 % to 35 % of newly diagnosed myeloma patients, 40 % to 60 % of patients with aggressive disease, and up to 85 % of patients with plasma cell leukaemia [8].

In total coherence with the literature, the chromosomal aberrations were highlighted in 23 % of MM cases in our study. All karyotypes of the aberrant clone in these patients were complex, similar to previous studies [1].

The most effective diagnostic method for examining chromosomal abnormalities, which are found in 90 % of cases, is fluorescence in situ

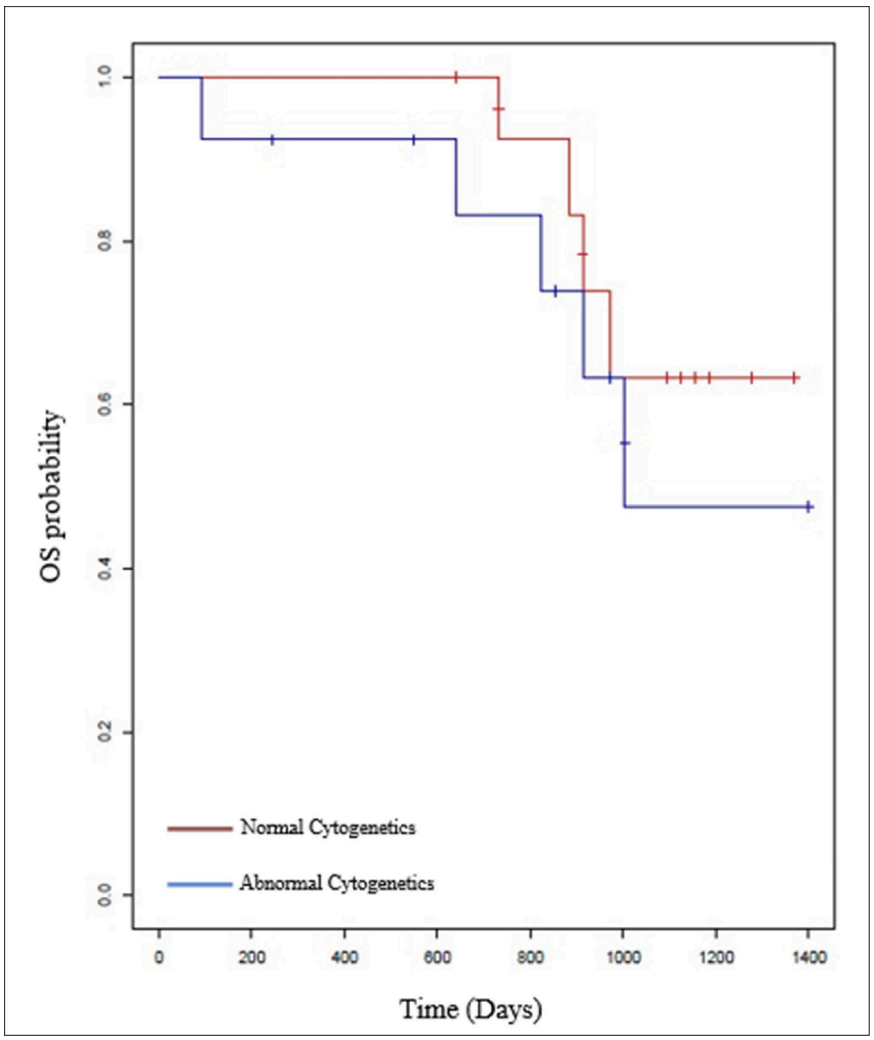

Fig. 3. Overall survival function according to the cytogenetic abnormalities.

hybridization [11]. It does not required active dividing cells as conventional cytogenetic does. However, it often requires a large amount of bone marrow and leads to technical requirements, including the sorting of plasma cells, which increases its cost, that are patients can't afforded.

Non-random, recurrent chromosomal abnormalities are common in multiple myeloma (MM) and include:

The translocation t (4;14) (p16; q32) involving the *IGH-MMSET / FGFR3* was first reported by Chesi [12]. It is detected in 10 %−15 % [13, 14], and constitutes nearly 20 % of the IgH translocations in multiple myeloma. This results in dysregulation of the oncogene *FGFR3* [13]. According to the IMWG and the updated International Staging System (ISS), it is classified as a high-risk cytogenetic abnormality [15,16].

The deletion of the chromosome 17 at the p13 locus which codes for the p53 tumor suppressor gene is considered a very important prognostic factor in MM [17,13]. It is seen in around 10 % of newly diagnosed MM patients [14,17], although the prevalence rises as the disease progresses [18]. The deletion 17p13 is considered a marker of poor prognostic.

Chromosome 1 abnormalities have been found to be a major prognostic indicator [19]. Interstitial deletions of 1p or amplifications of 1q are the most common chromosome 1 aberrations [19]. The most common structural abnormality in MM patients, gain of 1q21 (CKSIB gene), has been identified as an independent poor prognostic factor and is present in 35 %−40 % of MM patients [14].

In the present study, the 17p13 deletion, and 1q21 amplification are the most frequent structural chromosomal alterations, as each of these abnormalities were detected in 17 % of MM cases. The 14q32/*IGH* translocation is found in 20 %, 7 % of which represent the t (4;14).

In addition, microglobulin B-2 levels are higher in the group of patients with more complex cytogenetic abnormalities than in those with fewer abnormalities. Of all the prognostic factors studied, bone marrow plasma cell involvement is significantly higher in patients with cytogenetic abnormalities. The percentage of anomalies discovered had a positive correlation with both factors. These results support the idea that the aggressiveness of the disease is regularly correlated with the ability of traditional cytogenetic testing to identify an aberrant clone in myeloma.

The correlations between b2-microglobulin levels and the presence of complex abnormalities, 17p deletion and t (4;14) translocation confirm that these parameters are significant prognostic indicators, as seen in all previous studies.

Many studies have linked the t (4;14) and 17p deletion to shorter life expectancy [13]. A study published in 2017 found that patients with a complex karyotype with a p53 gene deletion have a significantly worse overall survival than patients with a normal karyotype with the same abnormality [20].

In our study, 46 % (14/16) of the cases analysed had a significantly worse overall survival (Fig. 3). Furthermore, 17 % of our patients with the p53 gene had extra aggressive characteristics, such as plasmacytomas and hypercalcemia [13]. All of this shows that even if p53 deletions are found at the time of diagnosis, they are most likely markers of an advanced clone [13].

5. Conclusion

This work is not only the first of its kind in our country to study the frequencies of recurrent cytogenetic abnormalities, and their importance on prognosis of MM patient, but it also revealed other many important findings.

They add to the growing body of data showing that MM is divised into subgroups of patients based on their underlying genetic abnormalities.

Moreover, it highlights the relationship between the aggressiveness of the disease and the complexity of chromosomal abnormalities. Finally, it determine the impact of cytogenetic abnormalities on clinical manifestations, and patient survival.

Statement of ethics

The internal ethics committee of the Cheikh Khalifa International University Hospital and the Mohammed VI University of Health Sciences (UM6SS), Casablanca, Morocco, approved the study.

All individual subjects involved in the study provided informed permission.

CRediT authorship contribution statement

Hasna Hamdaoui: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Writing – original draft. **Badreddine Nouadi:** Software. **Oumaima Benlarroubia:** Data curation. **Faiza Chbel:** Writing – review & editing. **Chaimaa Saadoune:** Writing – review & editing. **Faïza Bennis:** Writing – review & editing. **Afaf Lamzouri:** Writing – review & editing. **Fatima Chegdani:** Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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