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Negative prognostic significance of two or more cytogenetic abnormalities in multiple myeloma patients treated with autologous stem cell transplantation

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Malignant plasma cells in multiple myeloma (MM) are frequently characterized by complex karyotypes and chromosome instability. These cytogenetic changes are considered important prognostic indicators in MM patients. We have studied samples from 68 patients with newly diagnosed MM who were treated with high-dose chemotherapy and autologous stem cell transplantation. G-banding revealed abnormal karyotypes in 14 of 55 patients (25%) who had informative conventional cytogenetics. The combination of cytoplasmic immunoglobulin light chain labeling and interphase fluorescent *in situ* hybridization (cIg-FISH) revealed the presence of genetic aberrations in 53 of 68 patients (78%). Chromosome 13 abnormalities were found in 33 patients (50%) and IgH rearrangements in 36 patients (56.25%). In IgH positive patients we performed subsequent examinations of IgH affecting translocations t(4;14) and t(11;14) and we found translocation t(11;14) in 8 patients (12.5%) and t(4;14) in 10 patients (15.5%). The occurrences of others chromosomal abnormalities with known prognostic impact in MM were as follows: del(17)(p13) was present in 5 patients (9.8%) and gain 1q21 in 14 patients (36%). Analysis of survival of patients with different cytogenetic abnormalities revealed shorter overall survival (OS) in patients with IgH rearrangements (p=0.020) and trend to shorter OS in patients with gain 1q21 (p=0.064), respectively. Remarkably, patients with two or more aberrations had significantly shorter overall survival (p=0.001), time to progression (p=0.036) and progression free survival (p=0.008). Our results show a high incidence of chromosomal abnormalities in MM patients and confirm the prognostic impact of selected chromosomal aberrations as well as cumulative effect of multiple cytogenetic changes occurring simultaneously.

Key words: Multiple myeloma, FISH, chromosomal abnormalities, transplantation, chemotherapy

Multiple myeloma (MM) is the second most common haematological malignancy. It is characterized by malignant transformation and clonal proliferation of B-lymphocytes with the accumulation of malignant plasma cells in the bone marrow. The incidence of MM increases with age. The average age at presentation is 62 years in men and 61 years in women [1]. Patients below 40 years of age represent less than 3% of all cases. For many years, conventional chemotherapy with combination of melphalan and prednisone was the standard treatment, resulting in overall survival (OS) of approximately 3 years [2]. Currently, high-dose chemotherapy followed by autologous haematopoietic stem cell transplantation is recommended for patients below the age of 65 [3, 4]. This treatment extends the OS to 4–5 years [5], with approximately 28% of patients surviving 5 or more years [6]. Despite this relative treatment success, MM remains an incurable disease. Many prognostic factors for MM have been identified. The presence of numerical and/or structural chromosomal aberrations is one of the most important indicators for the prognostic assessments.

Due to low proliferation activity of MM cells, conventional cytogenetics detects chromosomal changes in as few as 26-40% of cases [7, 8]. In contrast, the technique of interphase fluorescent *in situ* hybridization (I-FISH) in combination with cytoplasm immunoglobulin staining or immunomagnetic separation of plasma cells enables detection of specific abnormalities in up to 86-98% of patients [9, 10, 11]. The most commonly encountered chromosomal aberrations

are del(13)(q14), IgH rearrangements, t(11;14), t(4;14), del(17)(p13) and gain 1q21. While each of these abnormalities has its own prognostic importance, simultaneous presence of several chromosomal aberrations itself is a particular strong prognostic factor for survival in MM.

We report on the prognostic significance of selected chromosomal alterations as well as the effect of various counts of aberrations on the OS outcome of MM patients treated with high-dose chemotherapy and autologous stem cell transplantation.

Patients and methods. We analyzed clinical and cytogenetic parameters in 68 patients with newly diagnosed MM treated with high-dose chemotherapy followed by autologous haematopoietic stem cells transplantation. Details of the treatment protocol were published previously by Krejci *et al.* [12]. All patients signed an informed consent with the study. The cohort of patients included 39 men and 29 women. The median age was 57 years (range 39-67 years). The median follow-up was 40 months (20.6-64 months). Baseline characteristics of the patients are summarized in Table 1.

Bone marrow samples were cultured for 24 hours in Panserin 441 at 37°C with 5% CO2. The cells were then treated by hypotonic potassium chloride solution, fixed in Carnoy fixative (methanol - acetic acid 3:1), and stored at -20 °C. The processed cells were centrifuged, overlaid with 96% ethanol, and used for cytogenetic studies.

Chromosomal G-banding. Metaphase slides were treated by trypsin (Sigma-Aldrich, Prague, Czech Republic) and stained by Giemsa solution to obtain chromosomal G-banding. The karyotypes were assembled according to ISCN 2005 [13].

Cytoplasmic immunoglobulin light chains labeling and interphase fluorescent in situ hybridization (cIg-FISH). Chromosomal abnormalities were detected in plasma cells using a combination of immunofluorescent labeling of cytoplasmic immunoglobulin light chains and interphase fluorescent *in situ* hybridization as described by Ahmann *et al.* [14] and modified in our laboratory. We analyzed the presence of del(13)(q14), del(17)(p13), gain 1q21, IgH rearrangements, t(4;14), and t(11;14). The following probes were used for I-FISH: LSI 13q14 (RB1) Spectrum Orange Probe, LSI p53 (17p13.1) Spectrum Orange Probe, LSI IGHC/IGHV Dual Color Probe, LSI IGH/FGFR3 Dual Color Probe, LSI IGH/CCND1 Dual Color Probe, and LSI 13q34 Spectrum Green and CEP 17 Spectrum Green reference probes (Abbott Vysis, Prague, Czech Republic). Gain 1q21 was detected using BAC DNA RP11-205M9 probe. Fifty to hundred plasma cells were evaluated for each sample. We used cut-off values recommended by the European Myeloma Network [15], i.e. 20% cut-off for deletions and numerical aberrations, and 10% cut-off for translocations and IgH rearrangements. An Olympus BX 61 (Olympus, Prague, Czech Republic) fluorescence microscope and a Vosskuhler 1300D CCD camera were used for image acquisition. Image analysis was carried out using LUCIA-KARYO/FISH software (Laboratory Imaging, Prague, Czech Republic).

Table 1. Baseline characteristics of patients

	N
Number of patients	68
Male	39 (57.4%)
Female	29 (42.6%)
Age at diagnosis (years)	
Median (range)	57 (39-67)
Follow up (months)	
Median (range)	40 (20.6-64)
Durie-Salmon clinical stage	
IA	6 (8.8%)
IB	1 (1.5%)
IIA	13 (19.1%)
IIIA	37 (54.4%)
IIIB	11 (16.2%)
Monoclonal immunoglobulin type	
IgG	38 (55.9%)
IgA	20 (29.4%)
IgD	1 (1.5%)
IgM	1 (1.5%)
B-J	6 (8.8%)
nonsecretory	1 (1.5%)
Beta2-microglobulin	3.15 (1.18-35.90)
Haemoglobin g/l	109.50 (65.70-153.0)
Calcium	2.43 (2.02-3.84)
Albumin g/l	36.6 (23.40-47.70)
C-reactive protein	2.50 (0.00-274.90)
LDH	5.36 (2.02-23.43)

LDH – lactate dehydrogenase

Statistical analysis. The statistical significance of differences in laboratory parameters was studied using the two-sample t-test or the Mann-Whitney test. The Mann-Whitney test was used for parameters with non-normal distribution, such as beta2-microglobulin, lactate dehydrogenase and C-reactive protein. The correlations between cIg-FISH results and the other variables such as serum biochemistry, treatment response, and ISS stage were calculated using the Fisher's test, the chi-square test, and the Kruskal-Wallis ANOVA test respectively. Survival analysis was carried out using the Kaplan-Meier method and the differences between subgroups were analyzed using the log rank test. **The level** of statistical **significance** was set to a p value of **0.05.**

Table 2. Conventional cytogenetic findings in MM patients

Patient number	karyotype
14	44,XY,+der(1),-4,der(8)t(8;20),-13,-20
17	45,XX,+3,del(6q),der(8p),del(10),-13,-16/46,XX [4]
18	46,XY,der(5),der(8),del(11q),der(20)t(5;20)
27	46,XY,t(11;14) [1] / complex changes /46,XY
28	44,XY,t(11;14),-13,-16(1)/46,XY
32	48,XY complex changes [10]
36	complex changes
52	complex changes
61	44,XY,del(6q),-13,der(14),-14
31	polyploidy [3] / 46,XY
33	53,XX,+2,+5,+11,+16,+19,+20,+21 [5]
39	44,XX,-19,-20 [5] / 46,XX [5]
40	46,XY(7)/53,XY(2) numerical only
41	45,XX,-13 (2)/ 46,XX(8)

Results

Occurrence of particular chromosomal aberrations. Conventional cytogenetics using G-banding detected abnormal karyotypes in 14 of 55 patients (25%) with informative results. Aneuploidy was seen in 5 cases of the total of 14 cases with chromosomal abnormality detected by conventional cytogenetics, and complex changes of karyotype in the other 9 patients (Table 2). Conventional cytogenetics was uninformative in remaining 13 patients.

cIg-FISH detected chromosomal changes in 53 of 68 patients (78%). Del(13)(q14) or monosomy of chromosome 13 was found in 33 of 66 analyzed patients (50%). IgH gene rearrangements were seen in 36 of 64 analyzed patients (56.25%). Samples with IgH rearrangements were investigated further in an effort to find the partner translocation gene. Using specific probes, t(11;14) was found in 12.5% (8/64), t(4;14) in 15.5% (10/64) patients, del(17)(p13) was observed in 9.8% (5/51) and gain 1q21 in 36% (14/39) of patients.

Simultaneous occurrence of multiple aberrations detected by cIg-FISH and associations between different chromosomal abnormalities. In 21 patients we observed only one chromosomal change, mostly either del(13)(q14) in 38% (8/21) or IgH rearrangement in 57% (12/21). A half of the IgH rearrangements was represented by translocation t(11;14). Translocation t(4;14) never occurred as a single aberration, similarly as del(17)(p13). 32 patients showed more than one cytogenetic abnormality. The most frequent combination was del(13)(q14) with IgH rearrangements, represented by translocation t(4;14) in 38% of cases. In 8 cases the next changes were del(17)(p13) and/or gain1q21.

There was observed a significant association between t(4;14) and del(13)(q14). About 90% of the patients with t(4;14) also carried del(13)(q14) (p=0.012). Del(17)(p13) and translocation t(4;14) were present simultaneously in 60% patients (p=0.035). No association was seen between gain 1q21 and other studied chromosomal aberrations.

Correlation between clinical data and FISH results. We analyzed correlations between standard clinical parameters including B2-microglobulin, LDH, serum calcium, CRP, haemoglobin, or serum albumin and presence of the studied chromosomal abnormalities. Del(13)(q14) was associated with lower serum albumin (p=0.007) and lower serum LDH levels (p=0.017). No statistically significant correlation was found between t(11;14), t(4;14), del(17)(p13) or gain 1q21 and any of the above clinical parameters.

Prognostic impact of chromosomal aberrations. The overall response rate (ORR) in our cohort was 94.5%, including complete response in 25% of cases, very good partial response in 37.5%, and partial response in 32% of patients. The presence or absence of detected chromosomal aberrations did not have any significant impact on the treatment response.

We did not observe any association between time to progression (TTP) and any of chromosomal abnormalities studied as separate changes. Patients with IgH rearrangement in myeloma cells had significantly shorter overall survival (37.3 months vs. not yet reached, p=0.020). Patients with gain 1q21 also had shorter OS, bordering on statistical significance (not yet reached vs. not yet reached, p=0.064). Other studied chromosomal abnormalities did not have a detectable influence on OS. These results are summarized in Figure 1.

Moreover, we analyzed the impact of presence of multiple chromosomal abnormalities on overall survival. Patients with 2 or more aberrations had significantly shorter overall survival as well as TTP and progression free survival (PFS) (OS: 36.7 months vs. not yet reached, p=0.001; TTP: 20.4 vs. 34 months, p=0.036; PFS: 18.1 vs. 32.2 months, p=0.008) (Figure 2).

Discussion

Findings of clonal chromosomal aberrations in plasma cells are considered as one of the most important prognostic factors in patients with multiple myeloma. In our study, conventional cytogenetics detected chromosomal aberrations in 25% of our cohort of 68 MM patients, what is in line with results published by Christensen *et al.* [8]. Analysis using interphase FISH combined with immunofluorescent labeling or immunomagnetic separation of plasma cells is known to have a higher sensitivity and finds chromosomal abnormalities in 86-98% of MM patients [9–11]. Using the technique of cIg-FISH for the detection of selected chromosomal abnormalities including del(13)(q14), del(17)(p13), gain 1q21, IgH rearrangements, t(11;14) translocation and t(4;14) translocation we have been able to detect at least one chromosomal alteration in 82% of our patients.

The frequency of studied chromosomal abnormalities in our patients was consistent with published data [16, 17].

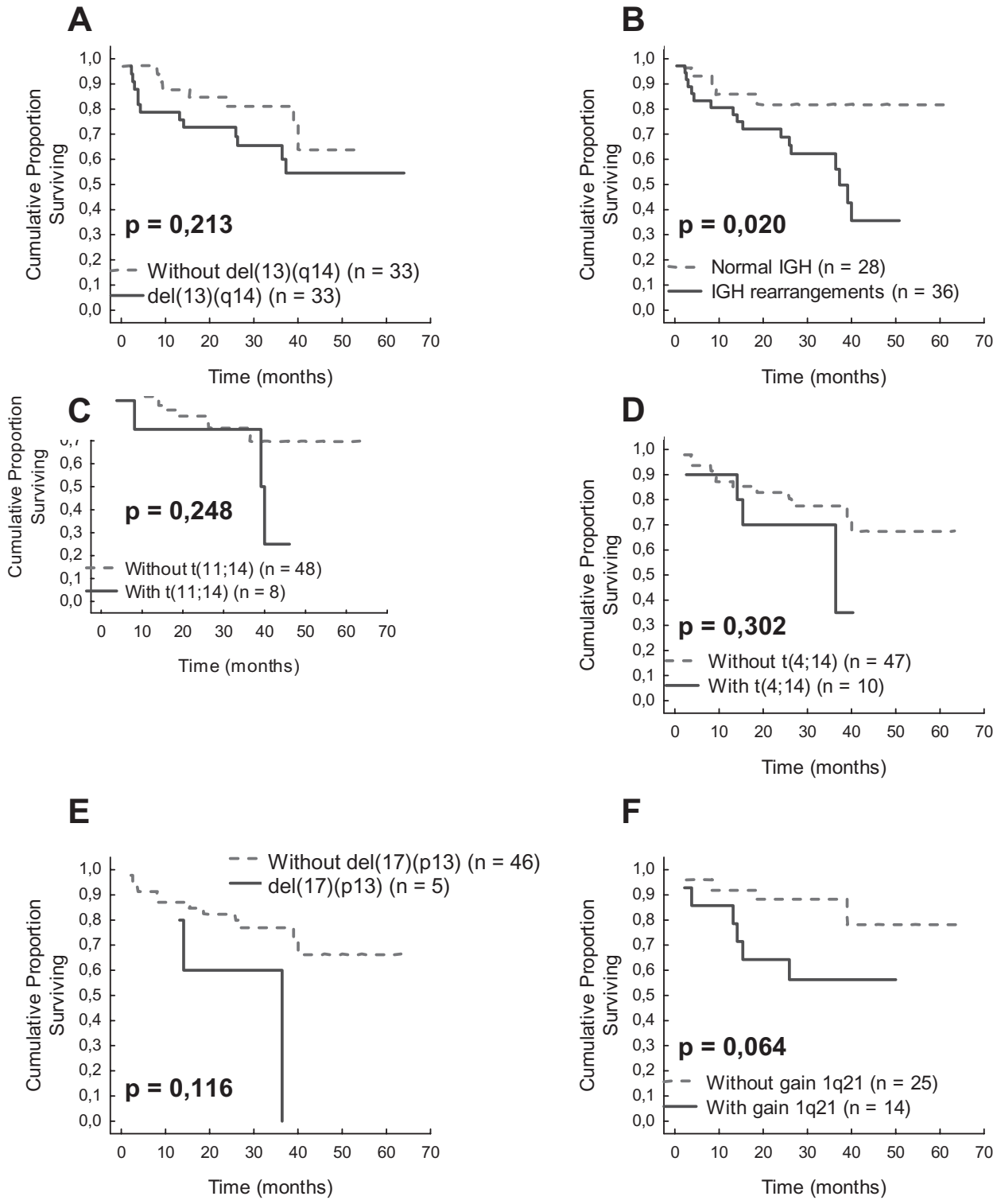

Figure 1. Prognostic significance of specific chromosomal abnormalities on overall survival of patients with MM. A. deletion of (13)(q14), B. IgH rearrangement (14)(q32), C. t(11;14), D. t(4;14), E. deletion of (17)(p13), F. gain 1q21.

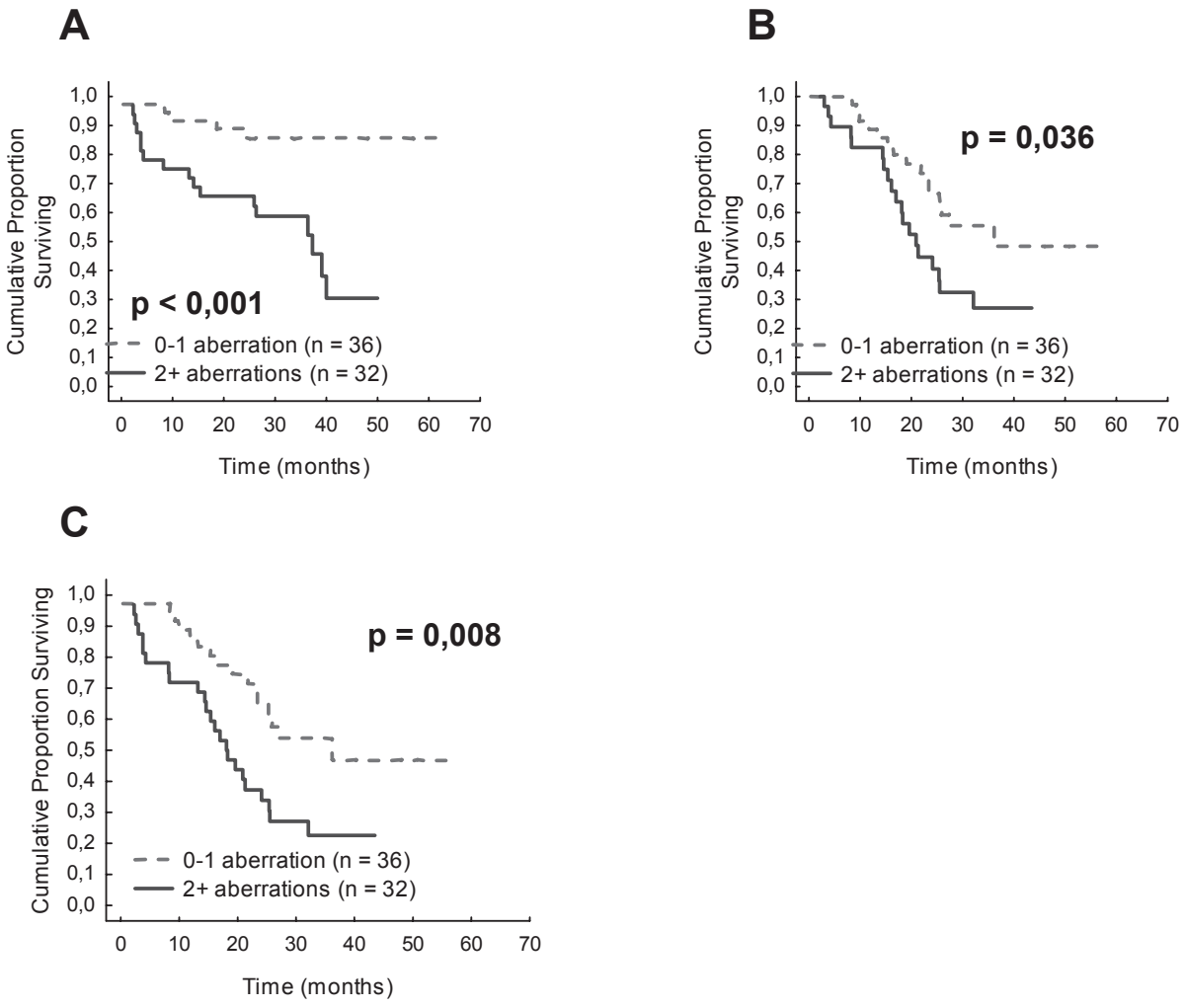

Figure 2. Impact of simultaneous occurrence two and more chromosomal abnormalities on A. overall survival OS, B. time to progression TTP, and C. progression free survival PFS.

The presence of chromosome 13 abnormalities detected by conventional cytogenetics is considered a negative prognostic factor in MM [16]. However, according to Gutierrez [18], del(13)(q14)/-13 detected by FISH as a sole abnormality would not represent a negative prognostic characteristic, in contrast to what had been previously widely assumed. Most of the prognostic power of del(13)(q14)/-13 was related to t(4;14) and del(17)(p13), which are frequently associated with del(13)(q14)/-13. In patients without t(4;14) and del(17)(p13), del(13)(q14)/-13 was no longer prognostic, whatever the cut-off chosen for its definition [19].

Chromosomal rearrangements involving the IgH switch region on chromosome 14 are ones of the most common chromosomal abnormalities in MM and can be detected in 50% - 70% of MM patients [20, 21]. IgH rearrangements are often found in up to 95% of malignant plasma cells and thus probably represent the primary genetic alterations. They are generally considered a marker of poor prognosis [22]. Several chromosomal partner sites have been described that participate in IgH translocation. The most commonly seen translocations are t(11;14), t(4;14), and t(14;16) which are found in 15%, 15%, and 5% of MM patients, respectively [11,23]. In our study, IgH translocations were detected in 56% of cases, including t(11;14) in 12% and t(4;14) in 15% of patients. We observed shorter overall survival in patients with IgH rearrangements. We have not been able to confirm the unfavourable impact of t(4;14) which has been reported by Avet-Loiseau *et al.* [19] and Fonseca *et al.* [20]. We found a statistically significant association between t(4;14) and RB1 deletion in accordance with findings published by the Avet-Loiseau group [24].

There is an evidence that del(17)(p13), which is found in approximately 10% of patients, is a marker of poor prognosis

[8, 20]. The incidence of del(17)(p13) in our cohort (9.8 %) was similar to that observed by others, that used 10% and 20% cut off, respectively. [5, 8]. According to recently published data, the presence of del(17)(p13) is associated with poor prognosis only if it is present in at least 60% of the malignant plasma cells [19]. In contrast, Gutierrez reported significantly shorter OS and TTP in patients with del(17)(p13) using an 8% cut-off [18]. If the cut-off of 60% were used, our analysis would be uninformative, as only two of our patients would be classified as positive.

Gain of the **long arm** of **chromosome** 1 is a novel prognostic important and common chromosomal abnormality in MM. Gain of the 1q21 region is found in approximately 31–72% of MM cases depending on stage of disease [25, 26, 27]. There have only been a handful of studies on the prognostic importance of gain 1q21 in patients with MM treated with autologous stem cell transplant. The incidence was 36% in our patients and gain 1q21 was the only studied chromosomal abnormality with a trend to shorter OS in our relatively small patient group (p=0.064). In our hands the presence of gain 1q21 did not correlate with the occurrence of any other of the studied chromosomal abnormalities in contrast to findings of Chen and collaborators who detected an association with del(13)(q14) [17]. Our next study carried out on more patients showed that gain1q21 is associated with significantly shorter OS intervals (p=0.001) [28]. Our results suggest that gain 1q21 is negative prognostic factor in MM patients.

Malignant plasma cells are characteristic by displaying a high degree of genetic instability with the simultaneous presence of multiple chromosomal abnormalities, which have been associated with poor survival. In agreement with these findings, in our study patients with two or more chromosomal abnormalities have significantly shorter survival than patients with one or none change (p=0.001). Similar results were described by Zemanova *et al.* [29]. In 38% of patients with 0-1 chromosomal changes was found only del(13)(q14) and therefore these patients reach longer OS than other patients with del(13)(q14) together with a t(4;14) and del(17)(p13) similarly with results published by Gutierrez et al. [18] a Avet-Loiseau *et al.* [19] Translocation t(4;14) and del(17)(p13) did not appear as singular changes in our cohort, only in combination with some of the above-mentioned aberrations. These findings confirm allegations that both these changes represent negative prognostic markers relating to progression of disease.

In addition, some researchers suggest that OS in MM patients is not influenced by the presence and type of chromosomal abnormalities but also, in an independent manner, on selected clinical parameters, such as beta2-microglobulin, ISS stage, and age [18, 19]. Because of the limited size of our cohort, multivariate analysis could not be carried out to answer this question.

In conclusion, I-FISH combined with immunofluorescent labeling of plasma cells is a useful method for the detection of chromosomal abnormalities in MM patients. In our study we have confirmed the unfavourable prognostic impact of IgH rearrangements and gain 1q21 on OS of MM patients treated with high-dose chemotherapy and autologous stem cell transplantation. Remarkably, we found cumulative effect of simultaneous presence of several chromosomal abnormalities, which is clearly connected with shorter overall survival as well as shorter time to progression.

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