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RESEARCH ARTICLE

Clinical characteristics and prognostic values of 1p32.3 deletion detected through fluorescence *in situ* hybridization in patients with newly diagnosed multiple myeloma: a single-center study in China

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Abstract **This study aimed to investigate the prevalence, clinical characteristics, and prognostic impact of 1p32.3 deletion in patients with newly diagnosed multiple myeloma (MM). A retrospective analysis was conducted on 411 patients with newly diagnosed MM; among which, 270 received bortezomib-based therapies, and 141 received thalidomide-based therapies. Fluorescence *in situ* hybridization (FISH) was performed to detect six cytogenetic abnormalities, namely, del(1p32.3), gain(1q21), del(17p13), del(13q14), t(4;14), and t(11;14). Results showed that 8.3% of patients with MM were detected with del(1p32.3) and had significantly more bone marrow plasma cells ($P = 0.025$), higher β2-microglobulin levels ($P = 0.036$), and higher lactate dehydrogenase levels ($P = 0.042$) than those without del(1p32.3). Univariate analysis showed that patients with del(1p32.3) under thalidomide-based therapies were strongly associated with short progression-free survival (PFS) (median PFS 11.6 vs. 31.2 months, $P = 0.002$) and overall survival (OS) (median OS 16.8 vs. 45.9 months, $P < 0.001$). Multivariate analysis revealed that del(1p32.3) remained a powerful independent factor with worse PFS ($P = 0.006$) and OS ($P = 0.016$) for patients under thalidomide-based treatments. Patients with del(1p32.3) under bortezomib-based treatments tended to have short PFS and OS. In conclusion, del(1p32.3) is associated with short PFS and OS in patients with MM who received thalidomide- or bortezomib-based treatments.**

Keywords 1p32.3 deletion; 1q21 gain; prognosis; multiple myeloma; FISH; bortezomib; thalidomide

Introduction

Multiple myeloma (MM) is characterized with clonal proliferation of plasma cells (PCs) in the bone marrow (BM), secretion of monoclonal immunoglobulin, and presence of osteolytic bone lesions. Although treatment strategies for MM have improved in the last decade, it remains an incurable disease. Genetic abnormalities are generally considered the important prognostic factors in patients with MM. Identification, characterization, and evaluation of the prognostic values of genetic abnormalities can contribute to individualize treatment [1,2].

A risk stratification system based on genetic indicators has been established and recommended by Mayo Clinic and International Myeloma Working Group (IMWG) [3,4]. Routine evaluation factors, such as del(17p13), t(4;14), and t(14;16) as detected through fluorescence *in situ* hybridization (FISH) [5] are clearly inadequate to explain the heterogeneity of patients with MM. Therefore, many cytogenetic abnormalities should be targeted for an accurate prediction of prognosis. Deletion of 1p has been identified as a common recurrent genetic event in MM (18%–38%). Several minimally altered regions on 1p, such as 1p32.3, 1p31.3, 1p22.1–1p21.3, and 1p12, have also been determined [6]. Studies have validated these deletions as independent negative prognostic factors [7–11].

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Chromosome 1p32.3 includes *CDKN2C*, which acts as a tumor suppressor gene. Thus, *CDKN2C* deletion may strongly affect cell-cycle regulation and MM pathogenesis [12,13]. Although 1p32.3/*CDKN2C* deletion has been identified as a prognostic marker, the clinical characteristics, response to therapies, and overall outcomes of patients with newly diagnosed MM exhibiting this abnormality have been poorly studied. In China, 1q21 gain probe is integrated into the FISH panel, and the identification of 1p32.3 deletion is not widely used.

We retrospectively analyzed 1p32.3 deletion status in 411 patients with newly diagnosed MM from a single center in China. Our objective was to evaluate the prevalence, clinical characteristics, and prognostic values of 1p32.3 deletion in these patients by using FISH. We assessed the 1p32.3 status under different stages of PC to determine whether 1p32.3 deletion is associated with disease progression.

Patients and methods

Patients

The single-center retrospective study included 411 patients with newly diagnosed MM, 18 patients with monoclonal gammopathy of undetermined significance (MGUS), and 40 patients with PC leukemia (PCL) from January 2006 to December 2016. MM diagnosis was established based on the IMWG diagnostic criteria. Written informed consent was obtained in accordance to the *Declaration of Helsinki*, and the protocol was approved by the hospital's institutional ethics review board.

A total of 270 patients received bortezomib-based initial therapies, which included bortezomib, cyclophosphamide, and dexamethasone or bortezomib, adriamycin, and dexamethasone. A total of 140 patients received thalidomide-based initial therapies, which included thalidomide, adriamycin, and dexamethasone or thalidomide, cyclophosphamide, and dexamethasone. After at least four cycles of treatments with partial remission or improved efficacy, the patients underwent consolidation therapy with their original regimen. Sixteen patients received allogeneic hematopoietic stem cell transplantation (allo-HSCT) or autologous-HSCT (auto-HSCT) after chemotherapy based on personal motivations.

FISH

Five commercial probes from Vysis (Vysis Downers, Grove, IL, USA) and one from Cytocell (Cytocell Ltd., Cambridge, UK) were used in FISH detection. PCs were purified by using CD138-conjugated magnetic beads based on the manufacturer's protocol (MiltenyiBiotec, Germany). FISH was conducted by using standard approaches to identify gain(1q21), del(1p32.3), del(17p), del(13q), t(11;14), and t(4;14). The cell sample was placed on a glass microscope slide, and the slide was immersed in 2 × SSC for 2 min at room temperature and dehydrated in an ethanol series (70%, 85%, and 100%) for 2 min. Then, 10 μL of probe mixture was added to the cell sample, covered with a coverslip, and sealed with rubber cement. The slide and probe were codenaturated at 73 °C for 3 min and hybridized at 37 °C overnight. After hybridization, the slide was washed and applied with 10 μL of DAPI. Fluorescent hybridization signals were observed by using an Olympus BX60 fluorescence microscope and captured on FISH 3.0 software. Only bright and easily detectable signals in FISH experiments were used in this study. A total of 200 nuclei were evaluated for each probe. Cut-off levels for positive results were estimated based on European Myeloma Network recommendations: 10% for the translocations and 20% for the deletions and gains [14]. All chromosome analyses were performed during diagnosis or before treatment.

Statistical analysis

Statistical analysis was performed on SPSS version 23.0 (SPSS Inc.). Categorical parameters were calculated either through Pearson's chi-square or Fisher's exact test. The distribution of continuous variables was calculated by using nonparametric Mann–Whitney U test. Progression free survival (PFS) and overall survival (OS) were determined, and the survival curve was plotted by using Kaplan–Meier method. The differences between survival curves were analyzed by using a log-rank test. Prognostic factors for survival were evaluated by using Cox's proportional hazards models for univariate and multivariate analyses. The variables with prognostic potential from the univariate analysis were inputted into the multivariate analysis. Tests were two sided, and P values < 0.05 were considered significant.

Results

Patient characteristics

The clinical and biological characteristics of 411 patients with newly diagnosed MM with or without del(1p32.3) are summarized in Table 1. The median age was 62 years (27–85 years), and the male/female ratio was 1.49 (246/165). The M-protein types observed in all patients were mainly IgG (197 or 47.9%) and IgA (107 or 26.0%). Overall, 119 (29.0%) were ISS I, 140 (34.1%) were ISS II, 146 (35.5%) were ISS III, and 6 (1.5%) were missing.

Table 1 Baseline clinical and biological characteristics of the evaluated patients with newly diagnosed MM

Characteristics	All patients	del(1p32.3) positive	del(1p32.3) negative	*P* value
Patients, *n* (%)	411	34	377	
Age (year); median (range)	62 (27–85)	64.5 (39–83)	62 (27–85)	0.806
Gender				0.205
Male, *n* (%)	246 (59.9)	24 (70.6)	222 (58.9)	
Female, *n* (%)	165 (40.1)	10 (29.4)	155 (41.1)	
ISS (*n* = 405)				0.053
I	119 (29.4%)	9 (30.0%)	110 (29.3%)	
II	140 (34.6%)	5 (16.7%)	135 (36.0%)	
III	146 (36.0%)	16 (53.3%)	130 (34.7%)	
BM Plasma cells (%); median (range)	26 (0–98)	40 (3–92)	24.5 (0–98)	0.025
Calcium (mmol/L); median (range)	2.25 (1.61–3.71)	2.36 (1.77–3.55)	2.24 (1.61–3.71)	0.235
β2-microglobulin (mg/L); median (range)	3.88 (0.73–76.63)	5.53 (2.0–76.63)	3.80 (0.73–39.08)	0.036
Creatinine (mmol/L); median (range)	80 (8–2013)	95 (43–923)	80 (8–2013)	0.166
LDH (U/L); median (range)	185 (59–1023)	232 (79–694)	183 (59–1023)	0.042
Ig isotype (*n* = 410)				0.173
IgG	197 (48.0)	13 (39.4)	184 (48.8)	
IgA	107 (26.1)	9 (27.3)	98 (26.0)	
IgM	4 (1.0)	1 (3.0)	3 (0.8)	
IgD	12 (2.9)	2 (6.1)	10 (2.7)	
Light chains	81 (19.8)	6 (18.2)	75 (19.9)	
Nonsecretory	9 (2.2)	2 (6.1)	7 (1.9)	
gain(1q21) (%)	222 (54)	192 (50.9)	30 (88.2)	<0.001
del(17p) (%)	30 (7.3)	21 (26.5)	9 (5.6)	<0.001
del(13q) (%)	157 (38.2)	138 (36.6)	19 (55.9)	0.041
t(11;14) (%)	33 (8.0)	31 (8.2)	2 (5.9)	1.000
t(4;14) (%)	34 (8.3)	32 (8.5)	2 (5.9)	1.000
Treatment				1.000
Bortezomib-based therapies	270 (65.7)	248 (65.8)	22 (64.7)	
Thalidomide-based therapies	141 (34.3)	129 (34.2)	12 (35.3)	

Ig, immunoglobulin; ISS, International Staging System; LDH, lactate dehydrogenase.

Chromosomal abnormalities in patients with MM

FISH analysis detected del(1p32.3) in 34 (8.3%) patients, 1q21 gain in 222 (54.0%) patients, del(13q14) in 157 (38.2%) patients, del(17p13) in 30 (7.3%) patients, t(4,14) in 34 (8.3%) patients, and t(11;14) in 33 (8.0%) patients. Among the patients, 135 (32.8%) do not have cytogenetic abnormality, 115 (28.0%) have one cytogenetic abnormality, and 161 (39.2%) patients have two or more abnormalities.

Correlation of 1p32.3 deletion with clinical and laboratory features

Strong correlations were observed between del(1p32.3) and 1q21 gain ($P < 0.001$), del(1p32.3) and del(17p) ($P < 0.001$), and del(1p32.3) and del(13q) ($P = 0.041$). Translocations t(4;14) and t(11;14) were not associated with 1p32.3 deletion (Table 1).

Patients with del(1p32.3) had significantly more BM PCs (median 40%) ($P = 0.025$), higher β2-microglobulin (β2-MG) levels (median 5.53 mg/L) ($P = 0.036$), and higher LDH levels (median 232 U/L) ($P = 0.042$) than those without del(1p32.3). del(1p32.3) was marginally associated with ISS ($P = 0.053$). No distribution difference was observed in age, gender, and Ig isotypes between patients with or without del(1p32.3) (Table 1).

Survival analysis

All follow-ups ended in July 2017, and the median follow-up was 21.6 months (1–141 months). Thirty-six (8.8%) patients did not complete the follow-up because of inconsistent contact information. A total of 130 patients died during the follow-up period. Univariate analysis showed that the presence of del(1p32.3), gain(1q21),

Table 2 Univariate analysis of risk factors on PFS and OS in patients with newly diagnosed MM

Risk factors	PFS		OS	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
del(1p32.3)	1.933 (1.260–2.966)	0.003	2.156 (1.324–3.511)	0.002
gain(1q21)	1.863 (1.396–2.486)	<0.001	2.176 (1.501–3.154)	<0.001
del(17p)	1.629 (1.034–2.566)	0.035	2.626 (1.625–4.244)	<0.001
del(13q)	1.588 (1.202–2.099)	0.001	1.449 (1.023–2.052)	0.037
t(11;14)	1.836 (1.166–2.891)	0.009	1.806 (1.054–3.096)	0.032
t(4;14)	1.560 (0.992–2.453)	0.054	1.487 (0.837–2.641)	0.176
ISS III	1.499 (1.129–1.991)	0.005	2.966 (2.085–4.219)	<0.001
Cr⩾177 mmol/L	1.949 (1.361–2.792)	<0.001	3.483 (2.310–5.252)	<0.001
Ca⩾2.75 mmol/L	1.551 (0.942–2.553)	0.084	2.292 (1.310–4.008)	0.004
LDH⩾240 U/L	1.523 (1.129–2.053)	0.006	1.602 (0.935–2.746)	0.086
Age⩾65	0.951 (0.718–1.260)	0.728	1.329 (0.941–1.878)	0.106

HR, hazard ratio; CI, confidence interval.

del(13q), del(17p), and t(11;14) was associated with substantially adverse PFS and OS. No significant difference was observed in PFS and OS for t(4;14) translocation (Table 2). Patients with del(1p32.3) had short PFS (median PFS 19.4 vs. 33.1 months, $P = 0.003$) and OS (median OS 27.7 vs. 48.7 months, $P = 0.002$). The Kaplan–Meier estimates of cytogenetic abnormalities on PFS and OS are illustrated in Fig. 1.

Significant difference was observed in the PFS and OS of patients with or without 1p32.3 deletion (median PFS 11.6 vs. 31.2 months, $P = 0.002$; median OS 16.8 vs. 45.9 months, $P < 0.001$) when the analysis was limited to those who received thalidomide-based treatments (Fig. 2). Patients with del(1p32.3) under bortezomib-based treatments had short PFS and OS (median PFS 19.4 vs. 33.3 months, $P = 0.136$; median OS 38.3 vs. 59.1 months, $P = 0.422$) but did not reach statistical significance. No significant difference was observed in the PFS of del(1p32.3)-positive patients under bortezomib- and thalidomide-based therapies (median PFS 19.4 vs. 11.6 months, $P = 0.212$). Patients with del(1p32.3) under thalidomide-based therapies had shorter OS compared with those under bortezomib-based therapies (16.8 vs. 38.3 months, $P = 0.008$) (Fig. 3).

According to multivariate analysis, 1p32.3 deletion remained the powerful independent adverse factor for the PFS ($P = 0.006$) and OS ($P = 0.016$) of patients under thalidomide-based therapies when the established prognostic variables, such as del(13q), del(17p), t(4;14), gain(1q21), t(11;14), ISS III stage, Cr, and LDH, were adjusted. gain(1q21) was an independent adverse risk factor for PFS but not for OS. del(13q14), del(17p), t(11;14), and t(4;14) were not independent prognostic factors for PFS and OS (Table 3). gain(1q21) was independently associated with significantly adverse PFS ($P = 0.013$) and OS ($P = 0.001$) for patients who received bortezomib-based treatments. del(17p13) was an independent adverse risk factor for OS but not for PFS. t(11;14) was an independent adverse risk factor for PFS but not for OS. By contrast, del(1p32.3), del(13q14), and t(4;14) were not independent prognostic factors for PFS and OS (Table 4).

The number of cytogenetic abnormalities significantly influenced PFS and OS. Median PFS was 64.6 months in patients with MM without abnormalities ($n = 135$), 29.6 months in patients with one abnormality ($n = 115$), and 23.5 months in patients with two or more abnormalities ($n = 161$) ($P < 0.001$). Median OS was not reached in patients with MM without abnormalities, whereas it was 46.6 months in patients with one abnormality and 37.4 months in those with two or more abnormalities ($P < 0.001$) (Fig. 4).

Detection of chromosome 1p32.3 deletion under different stages of PC dyscrasias

Eighteen patients with MGUS and 40 with PCL were included to compare the incidence of del(1p32.3) under different stages of PC dyscrasias. None of the 18 patients with MGUS had this deletion. However, the incidence of del(1p32.3) was 27.5% (11/40) in patients with PCL, which was relatively higher than that in the patients with newly diagnosed MM. These results indicated that the incidence of del(1p32.3) increased during the progression of PC dyscrasias from MGUS (0%) through MM (8.3%) to PCL (27.5%).

Discussion

In this single-center retrospective study, we defined the clinical characteristics and biological features of patients with newly diagnosed MM and 1p32.3 deletion as follows:

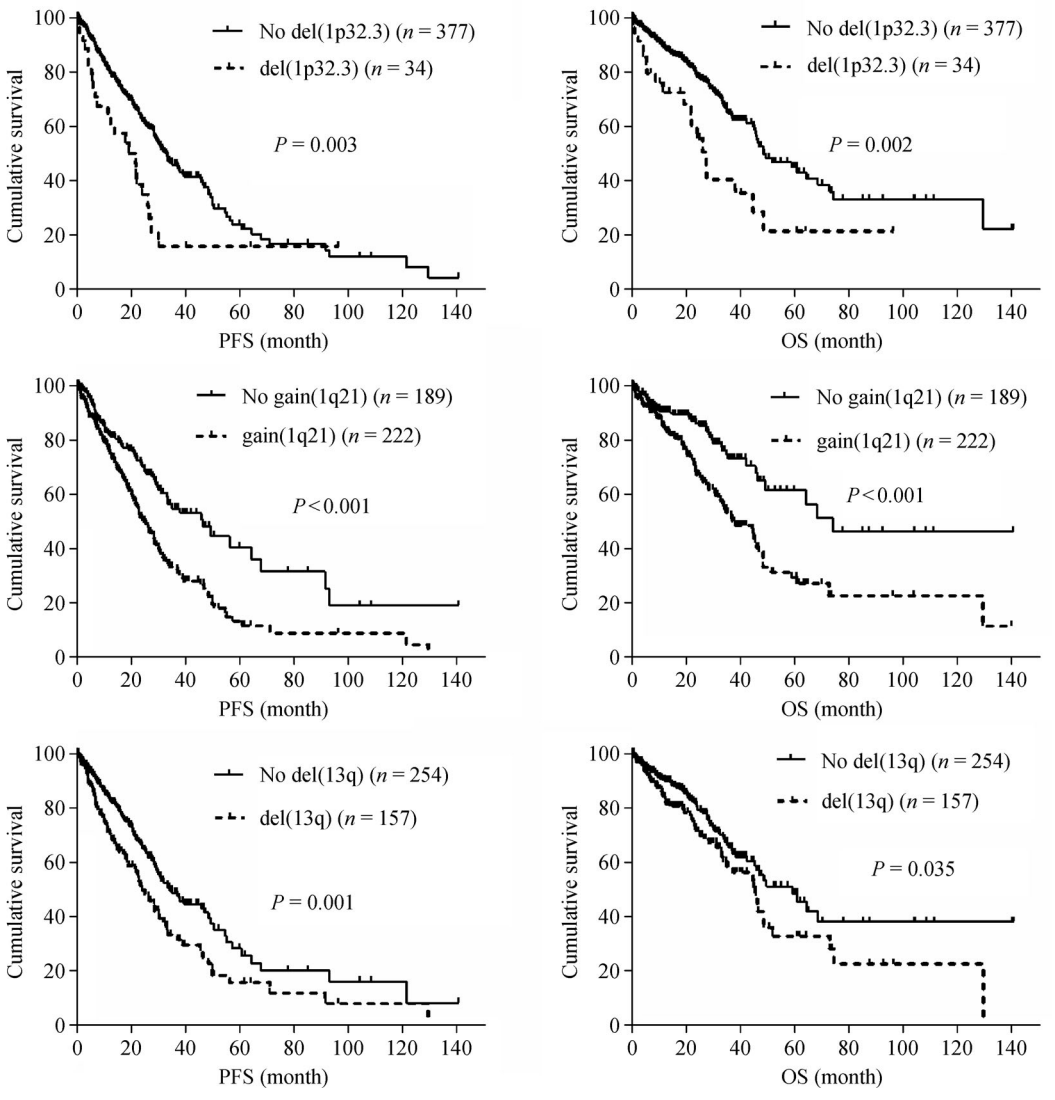

Fig. 1 Impact of cytogenetic abnormalities on PFS and OS.

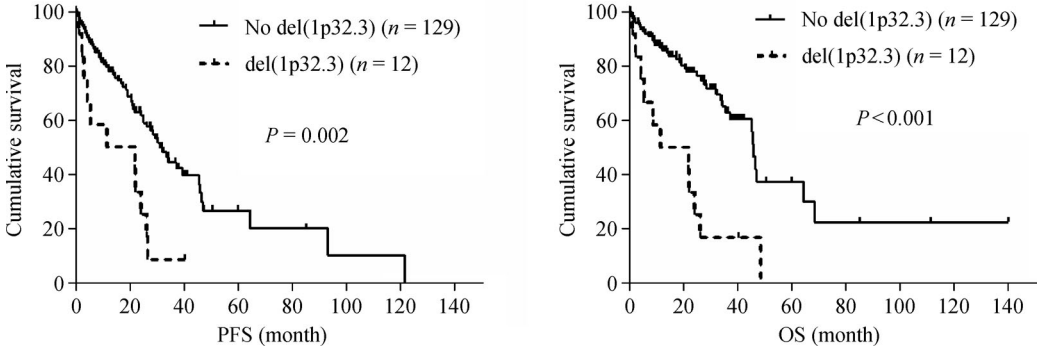

Fig. 2 PFS and OS of patients with or without del(1p32.3) under thalidomide-based therapies.

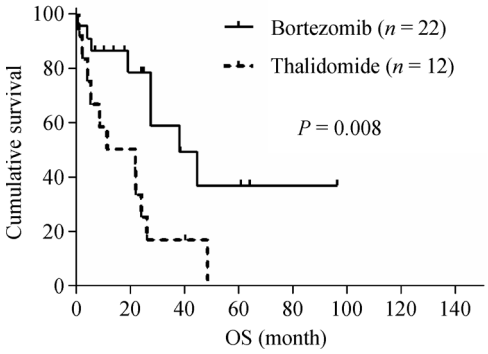

Fig. 3 OS of del(1p32.3)-positive patients under bortezomib-based or thalidomide-based therapies.

high number of BM PCs, β2-MG levels, and LDH levels. We confirmed the prognostic values of 1p32.3 deletion detected through FISH in patient with newly diagnosed MM who received bortezomib- or thalidomide-based therapies.

Our results showed that the 8.3% prevalence of 1p32.3/*CDKN2C* deletion in our MM series detected through FISH was consistent with the reported 7.3%–15% rate using the same technique [10–12,15]. In addition, del(1p32.3) was correlated with gain(1q21), del(17p), and del(13q). These results were partially comparable with those reported by Hebraud [10] and Li *et al*. [11], who showed that del(1p32) is correlated with t(4;14), del(13q), and del(17p). The correlation between del(1p32.3) and gain(1q21) and the absence of correlation between del(1p32.3) and t(4;14) observed in our cohort were due to the different sample sizes and features of patients.

The impact of 1p32.3 deletion on MM prognosis remains controversial. In this study, we confirmed that 1p32.3 deletion was associated with poor prognosis in newly diagnosed MM. The median OS of patients with 1p32.3 deletion was 27.7 months, which was comparable

Table 3 Multivariate analysis of genetic variables associated with PFS and OS in thalidomide-based therapies

Risk factors	PFS		OS	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
del(1p32.3)	3.083 (1.379–6.894)	0.006	2.478 (1.187–5.173)	0.016
gain(1q21)	2.019 (1.042–3.914)	0.037	1.509 (0.886–2.570)	0.130
del(17p)	2.134 (0.784–5.808)	0.138	2.680 (1.507–4.767)	0.568

Table 4 Multivariate analysis of genetic variables associated with PFS and OS in bortezomib-based therapies

Risk factors	PFS		OS	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
del(1p32.3)	1.263 (0.644–2.476)	0.497	0.626 (0.262–1.494)	0.291
gain(1q21)	1.702 (1.119–2.588)	0.013	2.536 (1.448–4.441)	0.001
del(17p)	1.330 (0.708–2.498)	0.376	3.255 (1.593–6.653)	0.001
t(11;14)	2.035 (1.162–3.564)	0.013	1.477 (0.743–2.937)	0.266

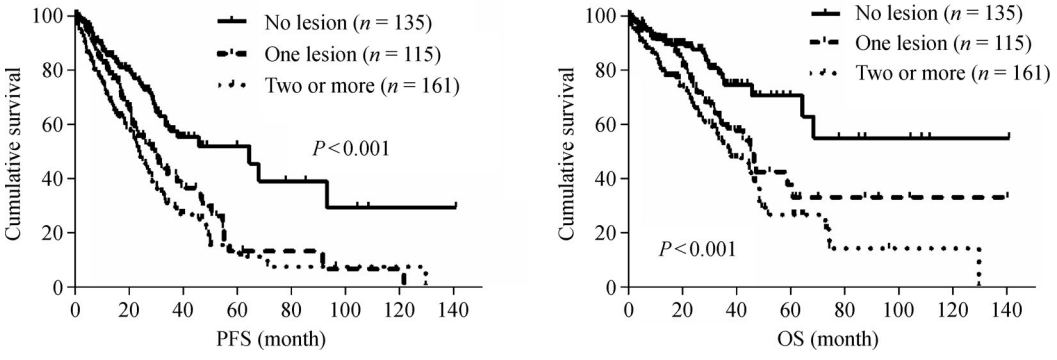

Fig. 4 PFS and OS of patients with MM without cytogenetic lesions, with one lesion, and with more than one lesion.

with the 26.7 months reported by Hebraud *et al*. [10]. We performed a subgroup analysis, and the results showed that del(1p32.3) was associated with impaired survival of patients under thalidomide-based treatments. These associations were confirmed in multivariate analyses, which included other genetic lesions. However, patients with del(1p32.3) under bortezomib-based treatments had short PFS and OS but did not reach statistical significance. This result may be because the sample size was small and thus should be enlarged. A previous study by Boyd *et al*. reported that 1p32.3 deletion is strongly associated with adverse prognosis in patients treated with ASCT, whereas its impact is neutral or slightly favorable in patients treated nonintensively [15]. Li *et al*. administered thalidomide- and bortezomib-based induction treatments to 128 and 138 patients with MM, respectively. However, OS analysis on del(1p32.3)-positive patients was not conducted in the two treatment groups because of the limited number of participants with this deletion. Future studies should be conducted to confirm the role of del(1p32.3) in the prognosis of two therapeutic strategies.

In our study, gain(1q21) remained the powerful independent prognostic factor for PFS and OS, and this finding was consistent with literature. del(17p) was independently associated with significantly adverse OS in bortezomib-based therapies because of the limited sample size of patients with del(17p), which influenced the statistical analysis.

t(11;14)-positive patients had shorter PFS and OS than t(11;14)-negative patients according to the univariate analysis. Existing observations suggested that patients with t(11;14) may have unfavorable outcomes compared with other standard risk patients [16,17]. The difficulty in establishing a favorable outcome for patients with t(11;14) may be related to the heterogeneity of patients with this genetic aberration [5]. t(4;14) translocation is considered a high risk marker [18,19]. However, in our study, no difference was observed in the PFS and OS of patients with and without t(4;14). Such result was because of the relatively short duration of follow-up, which was insufficient to detect the prognostic values in t(4;14) patients, the small sample size of t(4;14) patients, and the subsequent therapy to some extent. Future studies should be conducted to confirm the clinical significance of the two cytogenetic aberrations.

We observed that the number of cytogenetic abnormalities significantly influenced PFS and OS. Previous studies described similar results [20]. However, we were unable to analyze the impact of the co-occurrence of 1p32.3 deletion and other cytogenetic abnormalities on PFS and OS because of the limited sample size. Prospective studies should be conducted to investigate this subject.

In our study, the incidence of 1p32.3/*CDKN2C* deletion increased from MGUS through MM to PCL. This result was in accordance with previous findings [7]. However, the analyzed specimens were not paired samples, and no mechanical approach existed to delineate the underlying mechanism. Thus, the results should be systematically analyzed. Large samples at different stages of PC dyscrasias are required to confirm these results in future studies.

Our study had several limitations. First, this retrospective study had limited sample size, which had some impacts on our findings. Second, several different therapeutic regimens were used. Prospective studies should be conducted to confirm the role of del(1p32.3) in the prognosis of other therapeutic strategies, especially in patients treated with new drugs, such as bortezomib. Third, we did not provide experimental evidence to explain the molecular pathogenesis of 1p32.3/*CDKN2C* deletion in MM.

Our work identified the characteristics and prognostic values of 1p32.3 deletion in a relatively large cohort of patients with MM. del(1p32.3) was a negative independent prognostic factor in patients who received thalidomide-based therapies. Patients with del(1p32.3) under bortezomib-based treatments had short PFS and OS. Our study was a retrospective study, and our results should be confirmed in large sample size. Prospective works should improve the therapeutic management of patients with newly diagnosed MM and 1p32.3 deletion.

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Compliance with ethics guidelines

Huanping Wang, Haitao Meng, Jinghan Wang, Yinjun Lou, Yile Zhou, Peipei Lin, Fenglin Li, Lin Liu, Huan Xu, Min Yang, and Jie Jin declare that they have no conflict of interest with regard to this work. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the *Helsinki Declaration* of 1975, as revised in 2000 (5). Informed consent was obtained from all patients for being included in the study.

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