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Original Research Article

Additional genetic abnormalities significantly worsen poor prognosis associated with 1q21 amplification in multiple myeloma patients

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Abstract

We investigated the prognostic value of amp(1q21) alone and in combination with other abnormalities in newly diagnosed myeloma patients. The study group consisted of 104 patients treated with various induction regimens, mostly thalidomide based (87 patients). Amp(1q21) was detected in 49 (47.1%) of patients; in 26 (25.0%) cases, it was combined with del(13q14), in 7 (6.7%) with del(17p13) and in 15 (14.4%) with t(4;14)(p16;q32). The response rate was significantly better in amp(1q21)-negative than in amp(1q21)-positive patients (74.5% vs 55.1%, $p = 0.025$; complete response 18.2% vs 4.1%, $p = 0.024$). The median progression-free survival (PFS) was 33.9 months in patients without amp(1q21) and 10.3 months with this aberration ($p = 0.002$). The presence of additional abnormalities resulted in significantly shortened PFS when compared with patients with isolated amp (1q21): coexisting del(13q14) resulted in 7.8 vs 29.0 months of PFS ($p = 0.024$) and del (17p13) resulted in 4.0 vs 24.9 months of PFS ($p = 0.034$). The presence of amp(1q21) significantly influenced overall survival (OS) as well as PFS resulting in the median OS of 26.6 vs 62.4 months ($p = 0.018$) in patients without amp(1q21). The presence of additional genetic abnormalities significantly affected OS when compared with patients carrying isolated amp (1q21): for del(13q14) 18.9 vs 58.4 months ($p = 0.004$) and for del(17p13) 12.0 vs 46.5 months ($p = 0.036$). On multivariate analysis amp(1q21), del(13q14) and del(17p13) were found to be an independent adverse predictors of shorter PFS and OS. Our results showed that the presence of amp(1q21) was associated with poor prognosis. Moreover additional genetic abnormalities made PFS and OS further shortened.

Keywords: **Multiple myeloma; 1q21 amplification; prognosis**

Introduction

The survival of patients with newly diagnosed or relapsed/refractory multiple myeloma (MM) has increased in recent years following the introduction of novel therapies, such as immunomodulatory agents, for example thalidomide, lenalidomide and proteasome inhibitors, for example bortezomib [1]. However, the course of the disease demonstrates heterogeneity resulting in widely diverging survival times ranging from months to many years. Prognostic factors known for many years, such as beta-2-microglobulin, lactate dehydrogenase, haemoglobin concentration and International Scoring System (ISS) or Salmon-Durie staging, are very useful in predicting patient outcomes, but they do not fully explain such heterogeneity. For this reason, research of new prognostic factors is needed in order to determine the course of the disease, define therapeutic strategies and predict long-term survival and outcome.

Cytogenetic abnormalities are considered the major novel prognostic factors in newly diagnosed MM patients. Chromosomal aberrations are found in about 80–85% of MM patients, and some of them have been proved to predict patients' outcome. The most important chromosomal aberrations associated with unfavourable outcomes are hypodiploid genotype [2], amp(1q21), del(17p13), del (13q14) and translocations involving immunoglobulin heavy chain gene IgH located in chromosome 14q32. Chromosome 17p13 [3,4] and chromosome 13q14 [5,6] deletions have been shown to have adverse impact on survival in numerous series. Among immunoglobulin heavy chain gene aberrations, translocations t(4,14)(p16;q32) and t(14;16)(q32;q23) are most frequently reported to be associated with an unfavourable outcome [7,8]. Chromosome 1 abnormalities, mainly amp(1q21), are usually regarded as major prognostic factors in MM and their presence is associated with unfavourable disease course, shorter progression-free survival (PFS) and overall survival (OS) [9,10]. The presence of other high-risk genetic abnormalities coexisting with amp(1q21), like t(4;14)(p16;q32), del(17p13) or del (13q14) was shown

to have an additional impact leading to shorter survival in MM patients [11–13]. In our preliminary reports, we found the combination of amp(1q21) with other cytogenetic abnormalities to be an adverse prognostic factor in MM patients treated with thalidomide-based protocols [14,15].

In this study, we assessed the prognostic value of amp (1q21) alone and in combination with del(17p13), del (13q14) and t(4,14)(p16;q32) detected by fluorescence *in situ* hybridization (FISH) in newly diagnosed MM patients. The primary endpoints were response rates after first-line therapy, PFS and OS.

Methods

Patients

The study was conducted on a cohort of 104 patients with newly diagnosed MM subsequent to the approval from the Ethics Committee of the Medical University of Lublin. The group consisted of 48 men and 56 women: 65 patients had IgG monoclonal protein, 23 IgA and 16 light chain disease; light chain isotype was kappa in 60 cases and lambda in 44. At the time of diagnosis median age was 59 years (range 36–85) with 33 patients above 65 years, median serum beta-2-microglobulin concentration 3.3 mg/L (range 1.7–88.9 mg/L) and median haemoglobin concentration 9.6 g/dL (range 6.6–13.6 g/dL). Detailed clinical and laboratory features of patients are summarized in Table 1.

Table 1. Patients' characteristics

Characteristics	Median (range)	Number of patients (percentage)
Sex		
Male		48 (46.2)
Female		56 (53.8)
Age (years)	59 (36–85)	
>65 years		33 (31.7)
Haemoglobin (g/dL)	9.6 (6.6–13.6)	
Beta-2-microglobulin (mg/L)	3.3 (1.7–88.9)	
ISS prognostic index		
1		25 (24.0)
2		27 (26.0)
3		52 (50.0)
Monoclonal protein type		
IgG		65 (62.5)
IgA		23 (22.1)
Light chain disease		16 (15.4)
Light chain type		
Kappa		60 (57.7)
Lambda		44 (42.3)
Number of therapy lines	1 (1–7)	
1		55 (52.9)
2–3		33 (31.7)
>3		16 (15.4)
First-line therapy		
CTD		66 (63.5)
MPT		21 (20.2)
VAD		10 (9.6)
VMBCP		7 (6.7)
High-dose therapy with autologous stem cell support		
Yes		35 (33.7)
No		69 (66.3)

CTD, cyclophosphamide, thalidomide, dexamethasone; MPT, melphalan, prednisone, thalidomide; VAD, vincristine, adriamycin, dexamethasone; VMBCP, vincristine, melphalan, BCNU, cyclophosphamide, prednisone.

Interphase fluorescence *in situ* hybridization

Bone marrow aspiration samples were obtained from MM patients at diagnosis. The following probes were used: LSI 1q21/1p36 DNA Probe (Q-Biogene) for detection of amp (1q21), Vysis LSI RB1 DNA Probe and LSI 13q34 DNA Probe (Abbott Molecular) for detection of del(13q14) or monosomy of chromosome 13, Vysis TP53/CEP 17 FISH Probe Kit (Abbott Molecular) for detection of del(17p13), Vysis LSI IGH/FGFR3 DF FISH Probe Kit (Abbott Molecular) for detection of t(4;14)(p16;q32) and LSI D5S23/D5S721, CEP 9, CEP 15 Multi-colour Probe Set (Abbott Molecular) for ploidy determination.

Cultured bone marrow malignant plasma cells were identified using simultaneous staining of cytoplasmic immunoglobin and FISH (cIgFISH) according to the previously described protocol [16]. Analysis under fluorescent microscope was performed by scoring 100 Amca-positive plasma cells to determine the frequency of each aberration. The cut off level for all abnormalities was 20% according to the recommendations of the European Myeloma Network [17].

Treatment induction regimens

Patients were treated with different induction regimens, mostly CTD (cyclophosphamide, thalidomide, dexamethasone; 66 patients, 63.5%) and MPT (melphalan, prednisone, thalidomide; 21 patients, 20.2%); 87 (83.7%) patients received front-line thalidomide. Detailed description of treatment regimens is shown in Table 1. Among patients given CTD or vincristine, adriamycin, dexamethasone induction, 35 (33.7%) individuals received subsequent consolidation with high-dose therapy supported by autologous stem cell transplantation (HDT/ASCT).

Response evaluation and statistical analysis

Outcome measures included response to treatment, PFS and OS. Response to treatment was evaluated using International Myeloma Working Group uniform response criteria [18]. PFS was defined as the time elapsed between treatment initiation and tumour progression or death from any cause, and OS was defined as the time elapsed between treatment initiation and death.

The differences in response rates and the associations between the presence of amp(1q21) and other cytogenetic abnormalities were calculated using the Chi-square test. Univariate analysis was carried out to compare outcomes for cytogenetic factors. The Kaplan–Meier method was employed to calculate the survival analysis of PFS and OS. The differences between survival curves were analyzed using the log-rank test with $p < 0.05$ taken as the level of

Table 2. Incidence of genetic abnormalities

Genetic abnormality	Number of patients	Percentage
Ploidy		
H-MM	51	49.0
NH-MM	53	51.0
amp(1q21), including	49	47.1
combined with		
del(13q14)	26	25.0
del(17p13)	7	6.7
t(4;14)(p16;q32)	15	14.4
del(13q14)	47	45.2
del(17p13)	16	15.4
t(4;14)(p16;q32)	19	18.3
Complex abnormalities (≥3)	12	11.5

H-MM, hyperdiploid multiple myeloma; NH-MM, non-hyperdiploid multiple myeloma.

significance. Multivariate analysis of cytogenetic abnormalities associated with survival was performed using the proportional hazards regression model of Cox. The statistical analysis was performed using Statistica 6.0 software (StaSoft Inc, Tulsa, OK, USA).

Results

Incidence of genetic abnormalities

In the cohort of 104 patients, 51 (49.0%) had hyperdiploid MM (H-MM), and 53 (51.0%) had non-hyperdiploid MM (NH-MM). FISH analysis did not detect genetic abnormalities in 33 (31.7%) patients; 49 (47.1%) patients had amp (1q21); 47 (45.2%) patients had del(13q14); 19 (18.3%) patients had t(4;14)(p16;q32); and 16 (15.4%) patients had del(17p13). An isolated genetic abnormality was detected in 37 (35.6%) patients, two abnormalities in 22 (21.2%) patients, three abnormalities in 11 (10.6%) patients and four abnormalities in one (1.0%) patient. In 26 (25.0%) patients, amp(1q21) was combined with del (13q14), in seven (6.7%) with del(17p13) and in 15 (14.4%) with t(4;14)(p16;q32). The presence of amp (1q21) correlated significantly with del(13q14) and t (4;14)(p16;q32). Moreover, the distribution of examined abnormalities did not differ significantly in patients below and above 65 years, treated with and without thalidomide in first-line therapy, as well as given or not HDT/ASCT. The results of FISH analysis are summarized in Table 2 and Table 3.

Response to treatment

Out of a cohort of 104 patients the overall response rate following first-line therapy was confirmed in 68 patients (65.4%). The response was significantly better in patients without amp(1q21) than in patients with amp(1q21) detected by FISH: overall response rate was respectively 74.5% and 55.1% ($p = 0.025$), including complete response respectively 18.2% and 4.1% ($p = 0.024$) and very good partial response respectively 29.1% and 14.3% ($p > 0.05$). Moreover, the percentage of patients with progressive disease after first-line therapy was significantly higher in the group with amp(1q21) as compared with the amp(1q21)-negative group (28.6% vs 14.5%, $p = 0.041$). Results of first-line therapy in relation to the presence of amp(1q21) have been summarized in Table 4.

Progression-free survival

With a median follow-up of 16.5 months (range 1–53 months), 54 (51.9%) patients experienced progression, with a median PFS of 22.8 months. On univariate analysis, the median PFS estimated by the Kaplan–Meier method was 33.9 months in the group of 55 patients without amp (1q21) and 10.3 months in the group of 49 patients with amp(1q21) ($p = 0.002$). Negative impact of amp(1q21) was seen in both NH-MM and H-MM patients, although it was more obvious in patients with NH-MM. In H-MM patients without amp(1q21), the median PFS was not reached (59% probability to survive 14 months without progression), and in patients with amp(1q21), it was 23.5 months ($p > 0.05$); in NH-MM patients without and with amp(1q21), the median PFS was 35.2 months and 10.4 months, respectively ($p = 0.015$).

Table 4. Results of treatment after first-line therapy

Category of response	Patients without amp (1q21) (percentage)	Patients with amp (1q21) (percentage)	p
ORR	41 (74.5)	27 (55.1)	0.025
CR	10 (18.2)	2 (4.1)	0.024
VGPR	16 (29.1)	7 (14.3)	>0.05
PR	15 (27.3)	18 (36.7)	>0.05
SD	6 (10.9)	8 (16.3)	>0.05
PD	8 (14.5)	14 (28.6)	0.041

ORR, overall response rate; CR, complete response; VGPR, very good partial response; PR, partial response; SD, stable disease; PD, progressive disease.

Table 3. Associations of amp(1q21) with other cytogenetic abnormalities

	Patients with amp(1q21)			Patients without amp(1q21)			
Genetic lesion	Number with lesion	Total	Percentage	Number with lesion	Total	Percentage	p
del(13q14)	26	49	53.1	21	55	38.2	0.0482
del(17p13)	7	49	14.3	9	55	16.4	>0.05
t(4;14)(p16;q32)	15	49	30.6	4	55	7.3	0.008

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The presence of additional abnormalities other than amp (1q21) resulted in significantly shortened PFS. The median PFS for patients with amp(1q21) without del(13q14) was 29.0 months and for patients with amp(1q21) with del (13q14) 7.8 months ($p = 0.024$). Similar results were observed for del(17p13): patients with amp(1q21) without del(17p13) had the median PFS of 24.9 months, and patients with amp (1q21) with del(17p13) had the median PFS of 4.0 months ($p = 0.034$). The presence of t(4;14)(p16;q32) in addition to amp(1q21) also resulted in shortened PFS, although the difference was not statistically significant (median PFS 27.5 vs 10.2 months, $p > 0.05$). Moreover, the presence of complex abnormalities (at least three) was associated with significantly shortened PFS: the median PFS was 27.8 months for patients without and 6.9 months for patients with such abnormalities ($p = 0.003$).

Multivariate analysis was performed for eight covariates: age, thalidomide in first-line therapy, HDT/ASCT, ploidy status, amp(1q21), del(13q14), del(17p13) and t(4;14)(p16;q32). It confirmed amp(1q21), del(13q14) and del(17p13) as being independently associated with shorter PFS ($p = 0.016$, $p = 0.003$ and $p = 0.035$ accordingly) and HDT/ASCT with longer PFS ($p = 0.002$).

The Kaplan–Meier estimates of PFS are illustrated in Figure 1 and summarized in Table 5.

Overall survival

Forty-one (39.4%) patients died up to the time when the final analysis was performed. The median OS estimated by the Kaplan–Meier method in the whole group of 104 patients was 42.3 months. OS was 62.4 months in the group of 55 patients without amp(1q21) and 26.6 months in the group of 49 patients with this aberration ($p = 0.018$). The negative impact of amp(1q21) was significant in NH-MM. In this subgroup, the median OS in patients without and with amp(1q21) was 48.7 months and 16.4 months, respectively ($p = 0.006$). In

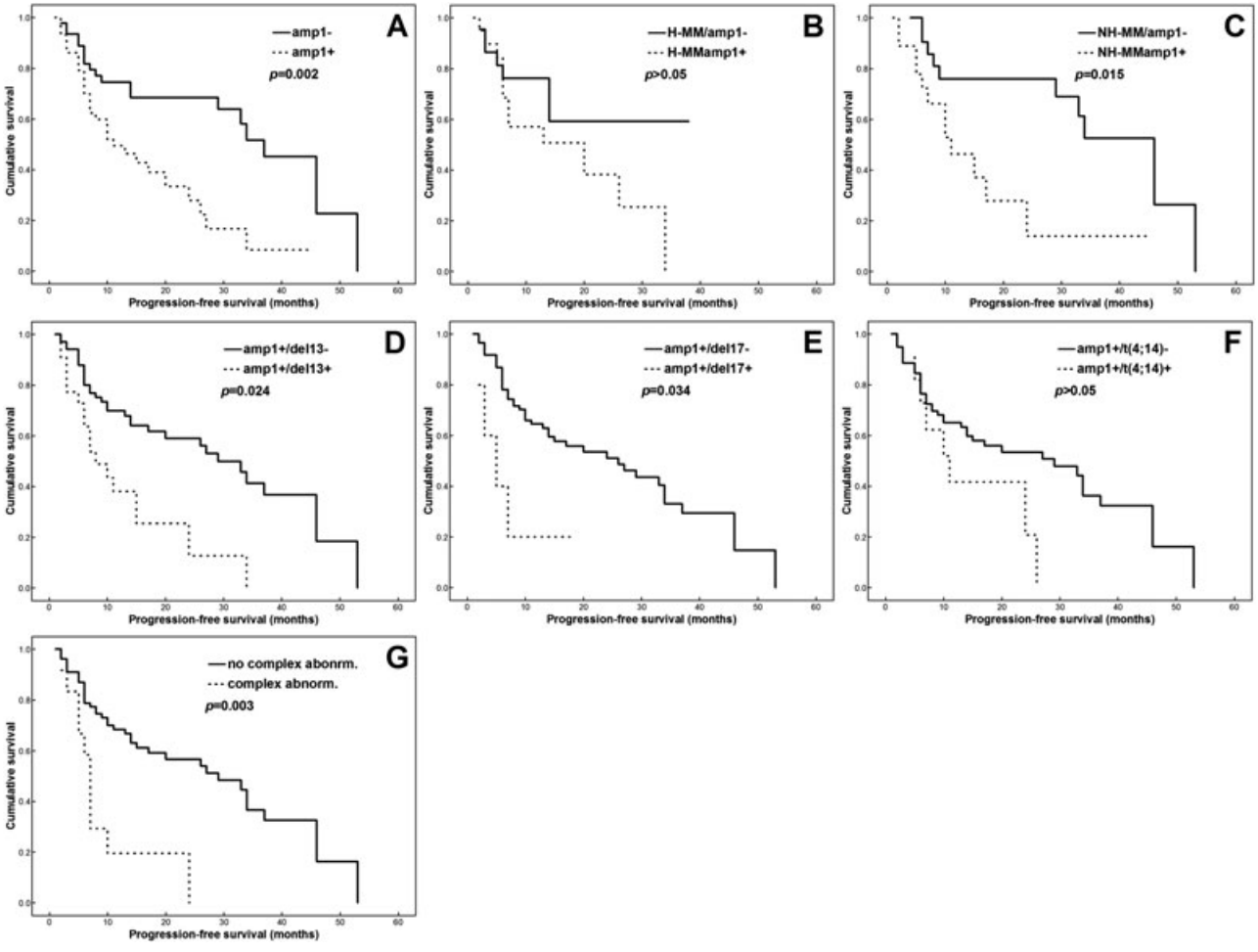

Figure 1. Progression-free survival (PFS) demonstrated by Kaplan–Meier curves. (A) Patients without amp (1q21) had the median PFS of 33.9 months, whereas patients with amp (1q21) had the median PFS of 10.3 months ($p = 0.002$). (B) Hyperdiploid MM (H-MM) patients without amp(1q21) had 59% of probability to survive 14 months without MM progression (median not reached), and H-MM patients with amp (1q21) had the median PFS of 23.5 months ($p > 0.05$). (C) In the non-hyperdiploid MM (NH-MM) subgroup, the median PFS for amp(1q21)-negative patients was significantly longer as compared with amp(1q21)-positive patients (35.2 vs 10.4 months, $p = 0.015$). (D). Patients with amp (1q21) without del(13q14) had the median PFS of 29.0 months, which was significantly longer as compared to patients with amp(1q21) accompanied by del(13q14) who had the median PFS of 7.8 months ($p = 0.024$). (E) The median PFS for amp(1q21) positive patients without del(17p13) was significantly longer as compared with amp(1q21)-positive patients with del(17p13) (24.9 v 4.0 months, $p = 0.034$). (F) The difference in the median PFS seen between amp(1q21)-positive patients without and with t(4;14)(p16;q32) was not statistically significant (27.5 vs 10.2 months, $p > 0.05$). (G) Patients complex genetic abnormalities (three or more) had the median PFS of 6.9 months, whereas patients without complex abnormalities had the median PFS of 27.8 months ($p = 0.003$)

Table 5. Impact of additional cytogenetic abnormalities detected by fluorescence *in situ* hybridization on progression-free and overall survival in patients carrying amp(1q21)

	Progression-free survival			Overall survival		
Genetic lesion	Lesion absent, median (months)	Lesion present, median (months)	*p*	Lesion absent, median (months)	Lesion present, median (months)	*p*
del(13q14)	29.0	7.8	0.024	58.4	18.9	0.004
del(17p13)	24.9	4.0	0.034	46.6	12.0	0.036
t(4;14)(p16;q32)	27.5	10.2	>0.05	43.8	27.5	>0.05

the H-MM subgroup, a negative impact of amp(1q21) on survival was observed, although it was not statistically significant: in H-MM patients without amp(1q21), the median OS was not reached (70% probability of surviving 17 months), and in patients with amp(1q21), it was 43.7 months ($p > 0.05$).

Similarly to PFS, the presence of additional genetic abnormalities significantly enhanced the negative influence of amp (1q21) on survival. The median OS for patients with amp (1q21) without del(13q14) was 58.4 months and for patients with amp(1q21) with del(13q14) 18.9 months ($p = 0.004$). The results were similar for del(17p13): patients with amp (1q21) without del(17p13) had a median OS of 46.5 months, and patients with amp(1q21) with del(17p13) had a median OS of 12.0 months ($p = 0.036$). Only the presence of t(4;14) (p16;q32) in addition to amp(1q21) did not result in statistically significantly shortened OS, although some difference was also observed (a median OS 43.8 vs 27.5 months, $p > 0.05$). The presence of complex abnormalities (at least three) was also associated with significantly shortened PFS. The median OS was 46.7 months for patients without and 15.3 months for patients with such abnormalities ($p = 0.049$).

On multivariate analysis HDT/ASCT, amp(1q21), del (13q14) and del(17p13) were found to be an independent predictors of shorter survival ($p = 0.011$, $p = 0.019$ and $p = 0.019$ accordingly) and HDT/ASCT of longer survival ($p = 0.001$).

The Kaplan–Meier estimates of OS are illustrated in Figure 2 and summarized in Table 5.

Discussion

Despite major advances in MM treatment following the introduction of novel agents such as immunomodulatory agents or bortezomib, the disease remains incurable. In recent years, genetic aberrations have emerged as the most important prognostic factors in MM, although their exact impact on response, disease course and survival, as well as the relationship among different aberrations, have not yet been fully understood.

One of the most common genetic abnormalities in MM are aberrations of chromosome 1, including amp(1q21). They are not specific to MM and can be found in many haematological malignancies and solid tumours. However, they are highly prevalent in MM and their frequency rises during the course of the disease. Amp(1q21) was found in 45% of patients with smouldering MM, 43% of patients with symptomatic MM at diagnosis and in 72% of patients with relapsed MM and was absent in patients with monoclonal gammopathy of undetermined significance [12]. In cases with chromosome 1q21 amplification, there is an enhanced expression of a cell cycle associated gene, CKS1B (cyclin kinase subunit 1B), and probably, it is responsible for the high proliferation rate [19], although it is also suggested that CKS1B overexpression is only the consequence of an advanced and genetically unstable disease [20].

Chromosome 1 abnormalities are regarded as the major prognostic factors in MM and their presence is associated with unfavourable disease course, shorter progression-free survival and overall survival. Despite limited number of patients included in presented study, we found 1q21 gain detected by FISH to be a very important adverse prognostic factor, which may reflect powerful impact of this genetic abnormality on survival of MM patients. Amp(1q21) was detected in 47.1% of patients with MM at diagnosis, and this result was consistent with other findings, in which the incidence of amp(1q21) was 38–45% [12,21,22]. In the cohort of 104 patients with MM, the presence of 1q21 gain resulted in significantly shorter PFS and OS. This negative impact on response duration and survival was particularly distinct in the subgroup of patients with NH-MM who had significantly shorter PFS and OS in the presence of amp (1q21), whereas in the H-MM group, the differences between amp(1q21)-positive and amp(1q21)-negative patients were not statistically significant. This observation may be explained by better prognosis associated with H-MM than with NH-MM, which has been demonstrated in numerous studies [23–27]. The adverse impact of amp (1q21) on MM patients' prognosis has been confirmed by many authors, and it can be seen in patients with newly diagnosed or refractory/relapsed MM, as well as in patients receiving HDT/ASCT. Newly diagnosed MM patients with amp(1q21) had inferior EFS and OS when compared with amp(1q21)-negative patients [12,21]. Application of HDT/ASCT did not change the poor prognosis in MM patients with amp(1q21) who were found to have significantly shortened PFS and OS [9,22], although the latter difference was not statistically significant in all series [9]. Similar results were obtained for the impact of chromosome 1p21 deletion [10], which was significantly correlated with amp(1q21) and both aberrations were poor prognostic factors in MM patients treated with HDT/ASCT [28]. Amp(1q21) was independent risk factor and its impact on both PFS and OS was not influenced by other abnormalities [22].

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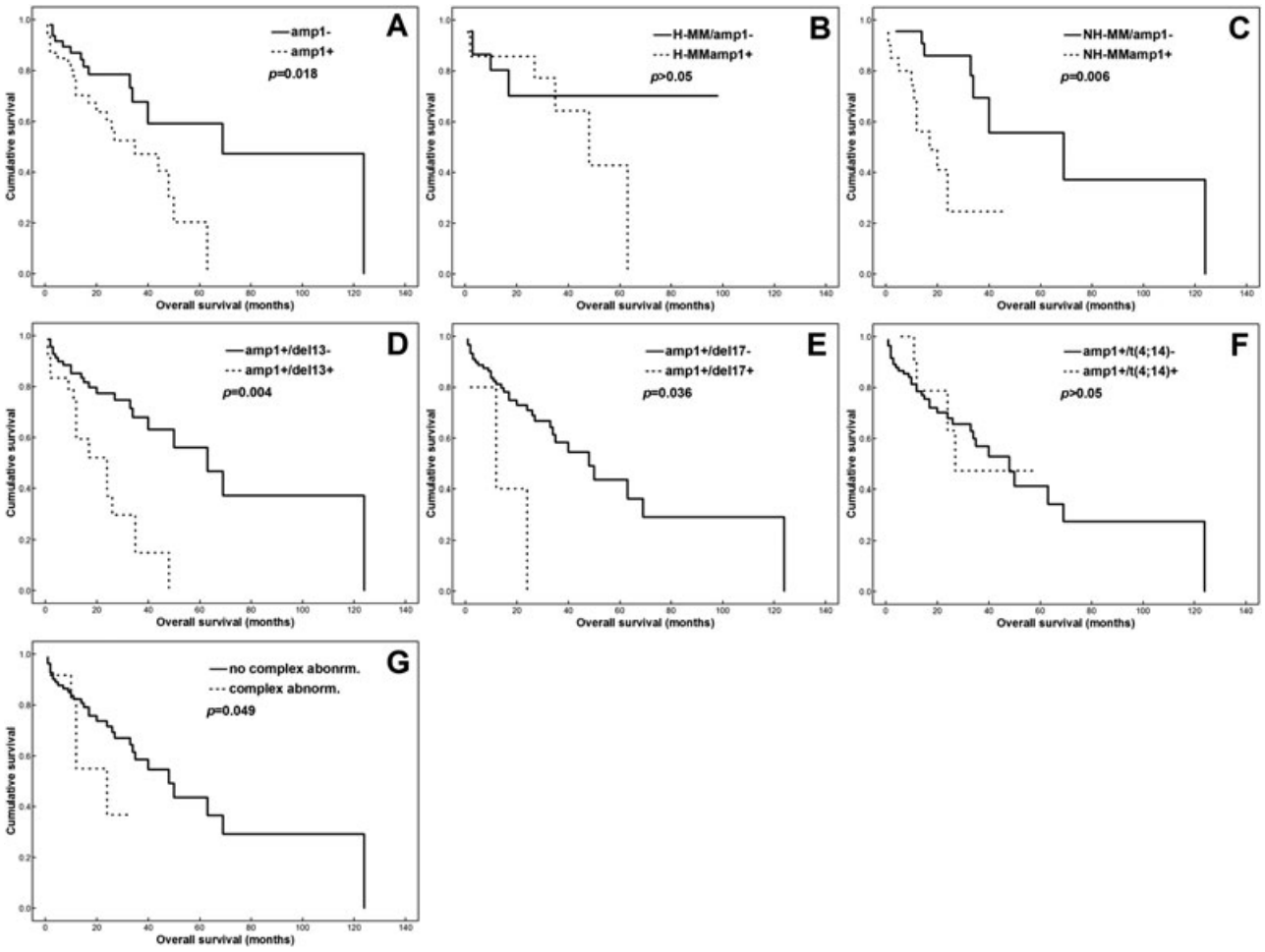

Figure 2. Overall survival (OS) demonstrated by Kaplan–Meier curves. (A) Patients without amp (1q21) had the median OS of 62.4 months, whereas patients with amp (1q21) had the median OS of 26.6 months ($p = 0.018$). (B) Hyperdiploid MM (H-MM) patients without amp(1q21) had 70% of probability to survive 17 months (median not reached), and H-MM patients with amp(1q21) had the median OS of 43.7 months ($p > 0.05$). (C) In the non-hyperdiploid MM (NH-MM) subgroup, the median OS for amp(1q21)-negative patients was significantly longer as compared with amp(1q21)-positive patients (48.7 vs 16.4 months, $p = 0.006$). (D) Patients with amp (1q21) without del(13q14) had the median OS of 58.4 months, which was significantly longer as compared to patients with amp(1q21) accompanied by del(13q14) who had OS of 18.9 months ($p = 0.004$). (E) The median OS for amp(1q21)-positive patients without del(17p13) was significantly longer as compared with amp(1q21)-positive patients with del(17p13) (46.5 vs 12.0 months, $p = 0.036$). (F) The difference in the median OS seen between amp(1q21)-positive patients without and with t(4;14)(p16;q32) was not statistically significant (43.8 vs 27.5 months, $p > 0.05$). (G) Patients complex genetic abnormalities (three or more) had the median OS of 15.3 months, whereas patients without complex abnormalities had the median OS of 46.7 months ($p = 0.049$)

Similar results were seen in clinical studies with refractory/relapsed MM patients. Amp(1q21) was found to be an independent prognostic factor for survival in this subset of patients treated with lenalidomide and dexamethasone, which resulted in significantly shorter PFS and OS [29,30]. Only bortezomib seems to be a unique agent overcoming the adverse impact of amp(1q21) on MM's course. In one series, amp(1q21)-positive patients with relapsed/refractory MM treated with bortezomib had similar response rate, PFS and OS to patients without this aberration [31], although other study conducted in greater cohort of refractory/relapsed MM patients given salvage therapy with bortezomib provided the opposite results with shorter PFS and OS in amp (1q21)-positive patients [32].

On the other hand, there are studies that did not confirm that 1q21 amplification was an independent adverse risk factor in multivariate model [11]. This discrepancy may be explained by the presence of numerous genetic aberrations that can be detected in MM patients and frequent coexistence of amp(1q21) with other high-risk genetic changes. Chromosome 1q aberrations were found to be commonly associated with del(13q14), del(17p14) and translocations involving immunoglobulin heavy chain gene located in chromosome 14q32 [10,11,22,30,31]. Recently, because of frequent coexistence of genetic changes, a novel prognostic model was proposed for MM patients with three groups of different prognosis: favourable-risk group defined by the absence of genetic aberrations, intermediate-risk group with one adverse aberration and a high-risk group with two or more adverse aberrations [33].

In this study, there was a significant correlation between amp(1q21) and del(13q14) as well as t(4;14)(16p;32q). These findings were reflected in the PFS and OS of patients carrying different aberrations in addition to 1q21 gain, and for almost all of the examined combinations, the difference was statistically significant. The presence of del(13q14) in

amp(1q21)-positive patients significantly shortened PFS and OS. Similar impact was seen with del(17p14). Additionally, PFS and OS were significantly shorter in patients with complex, that is, possessing three or more abnormalities, when compared with patients with two abnormalities or less. Only the presence of t(4;14)(16p;32q) patients did not change prognosis significantly in amp(1q21)-positive patients. Moreover, t(4;14)(16p;32q) was found to be only one among studied genetic abnormalities, which was not an independent risk factor of shortened PFS and OS. This observation may seem to be inconsistent with numerous reports and molecular classifications of MM [20], including recent analysis performed in a group consisting of more than 1000 patients [33]. On the other hand, we observed clear differences in median PFS and OS between amp(1q21)-positive patients with and without t(4;14)(16p;32q) in favour of the latter group (PFS 27.5 vs 10.2 months and OS 43.8 vs 27.5 months). Probably, the differences were not statistically significant because of limited number of patients and relatively short follow-up period, but one can speculate that after longer observation time and expanding the study group, also t(4;14)(16p;32q) could become statistically significant risk factor.

In summary, although our patients were a heterogeneous group as far as treatment regiments are concerned, including HDT/ASCT, a major conclusion that can be drawn from our study is that the presence of 1q21 gain is generally associated with poor prognosis. Our data clearly show that patients carrying amp(1q21) experienced worse treatment outcomes in terms of response rate, PSF and OS. When amp(1q21) was accompanied by other genetic abnormalities, like hypodiploidy, del(13q14) or del(17p13), the PFS and OS were further shortened, indicating synergistic impact of complex genetic abnormalities in MM patients.

Conflict of Interest

The authors indicate no potential conflict of interest.

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