original report

memo (2022) 15:90–93
https://doi.org/10.1007/s12254-021-00774-6

memo
magazine of european medical oncology

Clinical characteristics and prognostic value of 1q21 gain detected by fluorescence in situ hybridization in patients with newly diagnosed multiple myeloma

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Received: 10 August 2021 / Accepted: 21 October 2021 / Published online: 22 November 2021

Summary
Objectives This study aimed to investigate the clinical characteristics and prognostic impact of 1q21 gain in patients with newly diagnosed multiple myeloma (MM).
Methods This was a retrospective study of 197 patients with newly diagnosed MM. Fluorescence in situ hybridization was performed to detect six cytogenetic abnormalities: gain(1q21), del(17p), del(13q14), t(4;14), t(14;16), and t(11;14).
Results We showed that 57.8% of patients with MM had 1q21 gain. The patients with 1q21 gain had lower IgM (0.39 vs 1.14 g/L, $P=0.037$) and higher platelet count (177.62109/l vs 148.29109/l, $P=0.018$) than those without 1q21 gain, and were more likely to be accompanied by del(13q14) ($P<0.001$) or t(4;14) ($P=0.017$).
Conclusions We showed that 1q21 gain was associated with del(13q14) and t(4;14) increase, but it had no effect on prognosis of patients with newly diagnosed MM.

Keywords 1q gain/amplification · Prognostic · High-risk factors · Clinical characteristics · Chromosomal abnormalities

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Introduction

Multiple myeloma (MM) is a malignant B-cell disorder characterized by heterogeneous cytogenetic abnormalities, resulting in a wide heterogeneity in survival outcomes [1, 2]. Although treatment strategies for MM have improved in the last decade, it remains an incurable disease.

Karyotypes of malignant plasma cells are typically complex, containing numerous numerical and structural defects, including chromosomal translocations, deletions, duplications, and genetic mutations [3]. Detection of several cytogenetic abnormalities by interphase fluorescence in situ hybridization (FISH) is an important method for risk stratification. 1q21 gain is one of the most common cytogenetic abnormalities in MM [4]. About 30–50% of patients with newly diagnosed MM were positive for 1q21 gain [5, 6]. Previous studies have identified that some of the cytogenetic abnormalities largely determine the clinical heterogeneity of MM. Based on general consensus, hyperdiploidy, t(11;14), and a normal karyotype are standard-risk factors with a favorable prognosis, while t(4;14), t(14;16), and del(17p) are high-risk factors with an adverse prognosis [7–10]. However, within these cytogenetic abnormalities, the clinical prognostic value of 1q21 gain has been controversial. The prognostic significance of 1q21 gain in MM patients is always heterogeneous.

In this retrospective single-center study, we aimed to clarify the prognostic significance and the clinical features of 1q21 gain in patients with newly diagnosed MM.

Materials and methods

This retrospective study included 197 patients with newly diagnosed MM between August 2017 and Au-

Table 1 Clinical characteristics of multiple myeloma (MM) patients grouped by 1q21 gain or not

Clinical characteristics	Total	1q21 Gain (–)	1q21 Gain (+)	*p* value
N (%)	197	83	114	–
Age, mean (range)	66.5 (48–83)	71 (53–83)	56 (48–80)	0.659
Sex (%)	–	–	–	0.12
Male	118 (59.8)	55 (66.3)	63 (55.3)	–
Female	79 (40.1)	28 (33.8)	51 (44.7)	–
ISS (%)	–	–	–	0.62
I	40 (20.3)	19 (22.6)	21 (18.3)	–
II	66(33.5)	29(34.6)	38(32.2)	–
III	91(45.7)	36(41.7)	56(47.8)	–
DS (%)	–	–	–	0.488
IA	6 (3)	4 (4.8)	2 (1.8)	–
IIA	48 (24.4)	23 (27.7)	26 (22.8)	–
IIB	5 (2.5)	2 (2.4)	3 (2.6)	–
IIIA	92 (46.7)	32 (38.6)	60 (52.6)	–
IIIB	44 (22.3)	22 (26.5)	23 (20.2)	–
WBC	6.02 (0.89–52.17)	6.15 (2.21–21.3)	5.93 (0.89–52.1)	0.448
Hemoglobin (g/L), mean (range)	87.5 (34–167)	89.9 (34–166)	86.5 (38–167)	0.381
PLT (10^9/L), mean (range)	160.39 (18–476)	177.62 (36–476)	148.29 (13–429)	0.018*
Globulin (g/L), mean (range)	55.91 (13.5–137.6)	50.06 (15.1–103.0)	60.01 (13.5–137)	0.025*
Albumin (g/L), mean (range)	35.1 (17.0–55.0)	34.6 (17.0–55.0)	36.0 (17.4–51.0)	0.076
IgM (g/L), mean (range)	0.69 (0.05–35.4)	1.14 (0.05–35.4)	0.39 (0.05–5.18)	0.037*
IgA (g/L), mean (range)	8.77(0.7–83)	6.02(0.98–73.28)	7.21(1.2–83)	0.989
IgG (g/L), mean (range)	30.93(1.35–133)	28.13(2.04–133)	32.77(1.35–129.48)	0.516
Scr (μmol/L), mean (range)	159.9(39–1155)	173.3(39–1155)	136.2(40–653)	0.444
Ca^{2+} (mmol/L), mean (range)	2.45(1.52–15.6)	2.4(1.52–7.39)	2.4(1.5–15.6)	0.565
Serum b2-MG (mg/L), mean (range)	9.42 (0.39–57.7)	9.7 (0.39–57.7)	8.17 (1.36–46.5)	0.534
Lactate dehydrogenase (U/L), mean (range)	203 (54–659)	186.3 (55–612)	218 (64.8–659)	0.388
*Means $P < 0.05$				

gust 2019. All results of clinical tests during hospitalization were collected and analyzed through our electronic medical record system after the patients or their agents gave signed informed consent. The diagnosis of MM patients complied with the updated International Myeloma Working Group (IMWG) diagnostic criteria of 2014. For patients with newly diagnosed MM, we performed routine blood tests; liver and kidney function tests (including lactate dehydrogenase [LDH]); measurement of electrolytes, serum β2-microglobulin, serum free light chain, and serum immunoglobulins; serum immunofixation electrophoresis; light chain quantification; general X-ray plain radiography and positron emission tomography/computed tomography; bone marrow cytology smears and bone marrow biopsies; immunohistochemical staining; flow cytometry; and FISH detection of t(4;14)(FGFR3/IGH), t(11;14)(MYEOV/IGH), t(14;16)(MAF/IGH), 1q21 gain(CKS1B), del(17p)(TP53) and del(13q14)(FKHR). Durie-Salmon and International Staging System (ISS) stages were also evaluated. Selection criteria included: (1) received more than 4 cycles of chemotherapy, all patients were mainly treated with bortezomib and or thalidomide and dexamethasone as the main drug treatment plan, and consolidation and maintenance treatment after 4 courses of induction treatment; (2) did not receive stem cell transplantation (SCT).

Statistical analysis

The categorical clinical characteristics and cytogenetics were summarized as percentages, and continuous clinical characteristics were described as median and range. The X^2 test or two-sided Fisher's exact test was used to compare categorical clinical characteristics and cytogenetics between the groups. Overall survival (OS) was defined as the interval from initiation of therapy to death from any cause. The Kaplan–Meier method was used to plot the survival curves, with the log-rank test to assess the differences. SPSS version 22.0 (IBM Inc., Chicago, IL, USA) was used for all statistical analyses. Statistical significance was reached if the P value was <0.05. When there are significant confounding factors, both single-factor and multifactor analysis must be used, and the single factor with significant borderline significance ($P<0.2$) of the analysis result is selected for multifactor regression model (Cox regression model) analysis.

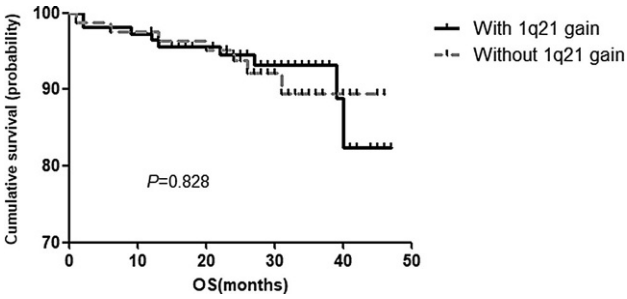

Fig. 1 Effects of 1q21 gain on survival. There is no significant difference in survival time between the groups with 1q21 gain and without 1q21 gain

Results

The final follow-up date was 30 December 2020, and the median follow-up time was 28.2 months (range 2–47 months). Among the 197 patients with newly diagnosed MM, 1q21 gain was detected in 114 (57.8%). Platelet count and IgM were associated with 1q21 gain. Compared with patients without 1q21 gain, patients with 1q21 gain tended to have lower IgM concentration (0.39 vs 1.14 g/L, $P=0.037$). The platelet count of patients with 1q21 gain was higher than that in patients without 1q21 gain (177.62×10^9 vs 148.29×10^9/l, $P=0.018$). Total globulin was higher in patients with 1q21 gain than in those without 1q21 gain (60.01 vs 50.06 g/l, $P=0.025$). There were no significant differences between patients with or without 1q21 gain for white blood cell count, hemoglobin, age, gender, Durie-Salmon stage, International Staging System stage, calcium, LDH, serum creatinine, albumin, and β2-microglobulin ($P>0.05$) (Table 1).

We also analyzed the combined effects of 1q21 gain and other cytogenetic abnormalities on patient outcomes. For the routine risk stratification mentioned above, del(17p), t(4;14), and t(14;16) were considered as high-risk cytogenetic factors in the following analysis. Patients were divided into two groups according to 1q21 gain. OS did not differ significantly between the two groups ($P>0.05$) (Fig. 1). Patients with 1q21 gain were more likely to be accompanied by del(13q14) ($P<0.001$) or t(4;14) ($P=0.017$) (Table 2). The most commonly combined genetic abnormality was del(13q14), which was found in 66.7% of patients with 1q21 gain.

Table 2 Correlation of 1q21 gain with other cytogenetic abnormalities in multiple myeloma (MM)

	1q21 Gain (–)	1q21 Gain (+)	*p* value
del (17p) (%)	9/83 (10.8)	9/114 (7.9)	0.478
del (13q14) (%)	30/83 (36.1)	76/114 (66.7)	<0.001*
t (11;14) (%)	13/83 (15.6)	14/114 (12.3)	0.567
t (4;14) (%)	25/83 (30.1)	54/114 (47.4)	0.015*
t (14;16) (%)	1/83 (1.2)	4/114 (3.5)	0.672

*Means $P<0.05$,

Discussion

This was a retrospective study of all MM patients treated in our hematological center. FISH analysis has been a routine detection method in newly diagnosed MM patients, whereas the prognostic role of 1q21 gain has been controversial. Many studies have found that 1q21 gain is one of the most frequent chromosomal aberrations in MM, with an occurrence rate of 30–50% [11, 12]. Therefore, it is necessary to study the biological characteristics and prognostic effects of 1q21 gain. In our study, 1q21 gain was identified in 57.8% of 197 patients, which is more than in previous studies. 1q21 gain was classified into the standard-risk category by IMWG consensus in 2014, whereas a low-risk classification must meet the criterion of absence of 1q21 gain [13]. Although 1q21 gain was not specially mentioned and was considered as standard risk in the 2013 Mayo mSMART consensus [14], Mayo mSMART 3.0 presented at the 2018 American Society of Hematology meeting classified 1q21 gain into the high-risk group. Therefore, opinions on the influence of 1q21 gain on prognosis are not consistent. One reason is addition to different treatment strategies, and another important reason is that the coexistence of other cytogenetic characteristics affects patients' outcomes. According to our data, patients with 1q21 gain had a higher incidence of del(13q14), t(4;14) than those without 1q21 gain, which supports the unfavorable biological characteristics of 1q21 gain from another aspect. Some previous studies have also reported the association between 1q21 gain and other cytogenetic characteristics [11, 15]. However, for patients with 1q21 gain, even with high-risk genetic abnormalities, there is no difference in survival time compared with patients without high-risk cytogenetics. This indicates that 1q21 gain combined with other cytogenetic abnormalities does not affect the prognosis of patients with high-risk genetics.

Another meaningful discovery was the clinical characteristics with 1q21 gain. Previous studies have shown that 1q21 gain is closely related to biological markers representative of tumor burden, such as β2-microglobulin, LDH, severe anemia, and advanced ISS stage [16, 17]. In our retrospective study, we did not find similar differences between the two groups of patients. Patients with 1q21 gain had lower levels of IgM and higher total globulin compared with those without 1q21 gain. The correlation between different IgM and 1q21 gain has rarely been reported. We found that patients with 1q21 gain had higher platelet count than those without 1q21 gain, which may have been due to their biological characteristics.

As a retrospective study, there were some limitations that should be considered. One major limitation was that only a small number of patients were evaluated. Therefore, it is difficult to determine whether 1q21 gain occurred as an additional increase in copy number, or was amplified more than the background

chromosomal gains. Further follow-up and larger prospective studies are needed to verify the results.

In summary, MM patients with 1q21 gain were characterized by lower IgM and higher platelet count than those without 1q21 gain, and were more likely to have accompanying del(13q14), t(4;14). 1q21 gain had no significant effect on OS in MM patients.

Acknowledgements We thank Cathel Kerr, BSc, PhD, from Liwen Bianji (Edanz) (www.liwenbianji.cn/) for editing the English text of a draft of this manuscript.

Funding This research did not receive any specific grant from funding agencies.

Conflict of interest X. Xiao, X. Fang, W. Yao and Z. Huaiping declare that they have no potential conflicts of interest. The authors have no relevant financial or non-financial interests to disclose.

References

1. Brigle K, Rogers B. Pathobiology and diagnosis of multiple myeloma. Semin Oncol Nurs. 2017;33(3):225–36.
2. Palumbo A, Avet-Loiseau H, Oliva S, Lokhorst HM, et al. Revised international staging system for multiple myeloma: a report from International MYELOMA working group. J Clin Oncol. 2015;33(26):2863–9.
3. Manier S, Salem KZ, Park J, et al. Genomic complexity of multiple myeloma and its clinical implications. Nat Rev Clin Oncol. 2017;14(2):100–13.
4. Byun JM, Dong-Yeop S, Junshik H, et al. Distinct predictive impact of FISH abnormality in proteasome inhibitors and immunomodulatory agents response: redefining high-risk multiple myeloma in Asian patients. Cancer Med. 2018;7(3):831–41.
5. Fonseca R, Van Wier SA, Chng WJ, et al. Prognostic value of chromosome 1q21 gain by fluorescent in situ hybridization and increase CKS1B expression in myeloma. Leukemia. 2006;20(11):2034–40.
6. Cremer FW, Bila J, Buck I, et al. Delineation of distinct subgroups of multiple myeloma and a model for clonal evolution based on interphase cytogenetics. Genes Chromosom Cancer. 2005;44(2):194–203.
7. Fonseca R, Blood EA, Oken MM, et al. Myeloma and the t(11;14)(q13;q32); evidence for a biologically defiffined unique subset of patients. Blood. 2002;99:3735–41.
8. Drach J, Ackermann J, Fritz E, et al. Presence of a p53 gene deletion in patients with multiple myeloma predicts for short survival after conventional-dose chemotherapy. Blood. 1998;92:802–9.
9. Chiecchio L, Protheroe RKM, Ibrahim AH, et al. Deletion of chromosome 13 detected by conventional cytogenetics is a critical prognostic factor in myeloma. Leukemia. 2006;20:1610–7.
10. Decaux O, Lodé L, Minvielle S, et al. Genetic abnormalities in multiple myeloma: role in oncogenesis and impact on survival. Rev Med Interne. 2007;28:677–81.
11. Avet-Loiseau H, Attal M, Campion L, et al. Long-term analysis of the IFM 99 trials for myeloma: cytogenetic abnormalities [t(4;14), del(17p), 1q gains] play a major role in defining long-term survival. J Clin Oncol. 2012;30(16):1949–52.
12. Smol T, Dufour A, Tricot S, et al. Combination of t(4;14),del(17p13), del(1p32) and 1q21 gain FISH probes identifies clonal heterogeneity and enhances the detection of adverse cytogenetic profiles in 233 newly diagnosed multiple myeloma. Mol Cytogenet. 2017;10:26.
13. Chng WJ, Dispenzieri A, Chim C-S, et al. IMWG consensus on risk stratification in multiple myeloma. Leukemia. 2014;28(2):269–77.
14. Mikhael JR, Dingli D, Roy V, et al. Management of newly diagnosed symptomatic multiple myeloma: updated Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) consensus guidelines 2013. Mayo Clin Proc. 2013;88(4):360–76. https://doi.org/10.1016/j.mayocp.2013.01.019.
15. Nemec P, Zemanova Z, Greslikova H, et al. Gain of 1q21 is an unfavorable genetic prognostic factor for multiple myeloma patients treated with high-dose chemotherapy. Biol Blood Marrow Transplant. 2010;16(4):548–54.
16. Avet-Loiseau H, Attal M, Moreau P, et al. Genetic abnormalities and survival in multiple myeloma: the experience of the Intergroupe Francophone du Myelome. Blood. 2007;109(8):3489–95.
17. Bang SM, Kim YR, Cho HI, et al. Identification of 13q deletion, trisomy 1q, and IgH rearrangement as the most frequent chromosomal changes found in Korean patients with multiple myeloma. Cancer Genet Cytogenet. 2006;168(2):124–32.