Impact of bortezomib on 1q21+ in multiple myeloma: A meta-analysis of treatment outcomes and prognostic implications

XIAONA ZHENG, SIYU LIN, KEJIE LU, JIAN HOU and TINGTING LIU

Department of Hematology, Renji Hospital, School of Medicine, Shanghai Jiaotong University, Shanghai 610041 P.R. China

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Abstract. The gain of chromosomal region 1q21 is a significant risk factor in multiple myeloma (MM) and is associated with poor prognosis. The introduction of bortezomib has notably improved outcomes for patients with MM. However, recent studies have reported conflicting results regarding the efficacy of bortezomib in mitigating the adverse effects of 1q21 aberration in these patients. To address this, in the present study, a meta-analysis was conducted based on 6 studies encompassing 1,575 patients with MM. The prognosis of patients with 1q21+ who underwent treatment with a bortezomib-based regimen was evaluated in terms of complete response (CR), overall survival (OS) and progression-free survival (PFS) rates. The results demonstrated that patients with 1q21 aberration were more likely to achieve CR than those without 1q21+ under bortezomib-based treatment [odds ratio, 0.64; 95% confidence interval (CI), 0.49-0.83; P=0.0008]. However, 1q21+ remained a high-risk factor in patients with MM even after bortezomib treatment [PFS: hazard ratio (HR), 1.72; 95% CI, 1.53-1.93; P<0.00001; and OS: HR, 1.95; 95% CI, 1.58-2.42; P<0.00001]. In conclusion, although bortezomib improved the likelihood of achieving CR in patients with 1q21+, this genetic aberration continues to be considered a high-risk factor in patients with MM treated with a bortezomib-based regimen.

Introduction

Multiple myeloma (MM) is the second most common hematological malignancy and is characterized by the abnormal proliferation of plasma cells in the bone marrow (1-3). The heterogeneous nature of MM results in varied response rates and survival outcomes among patients receiving identical treatments (4,5). Given that MM remains incurable, accurate risk stratification is essential for evaluating patient prognosis and determining optimal treatment strategies.

Cytogenetic abnormalities are critical prognostic factors in patients with MM. Among these, 1q21+ is one of the most frequently observed chromosomal aberrations, occurring in ~40% of newly diagnosed MM cases and 70% of relapsed/refractory cases (6). Previous studies have consistently identified 1q21+ as a poor prognostic marker and a high-risk factor in patients with MM (7-9). The introduction of novel drugs, including the proteasome inhibitor bortezomib, has significantly improved the prognosis of patients with MM (10). While some studies suggest that bortezomib may alleviate the negative impact of 1q21 aberration (11,12), others report conflicting outcomes (13,14). Therefore, a systematic review is necessary to clarify the prognostic significance of 1q21+ in patients with MM undergoing bortezomib-based treatment.

Relying solely on individual studies often fails to yield definitive conclusions. By contrast, meta-analyses have the potential to overcome the limitations of single studies by consolidating findings from multiple sources and resolving discrepancies. Therefore, a meta-analysis was conducted in the present study to evaluate the prognostic significance of 1q21+ in patients with MM undergoing bortezomib-based treatment.

Materials and methods

Literature screening to identify related studies. The present meta-analysis was conducted following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (15). In the present study, two authors independently screened relevant studies from the Embase (http://www.embase.com), PubMed (http://pubmed.ncbi.nlm.nij.gov/) and Cochrane Library databases (http://www.cochranelibrary.com). The search was restricted to publications in English and included studies published from inception until April 1, '23. The search focus was on studies that compared survival rates or response rates between patients with and without the 1q21+ aberration who underwent bortezomib-based treatment. The search strategy used various combinations of the following keywords: (((+1q21) OR (Gain(1q))) OR (Amp(1q))) OR (Chromosome 1 abnormality)) AND (bortezomib).

Correspondence to: Professor Jian Hou or Professor Tingting Liu, Department of Hematology, Renji Hospital, School of Medicine, Shanghai Jiaotong University, Shanghai 610041, P.R. China
E-mail: houjian@medmail.com.cn
E-mail: liutingting_0131@sina.com

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Inclusion and exclusion criteria. The inclusion criteria for the present study were as follows: i) Studies investigating the prognostic significance of 1q21+ in patients with MM treated with bortezomib; ii) administration of bortezomib-based treatment to patients; iii) division of patients into two groups based on the presence or absence of 1q21+; iv) inclusion of at least one of the following three indicators for analysis: Overall survival (OS), progression-free survival (PFS) or complete response (CR) rate; and v) publication in a peer-reviewed journal. The exclusion criteria were as follows: i) Reviews, meeting abstracts and letters that did not include a full text in English; ii) non-human studies; and iii) studies lacking usable data.

Data extraction from the related studies. The first two authors independently extracted detailed data, including the first author, year of publication, country, sample size, OS, PFS and CR rate. In cases where discrepancies arose during the data extraction process, consensus was reached through discussion with another author.

Quality assessment. The quality of the included studies was independently evaluated by two investigators using the Newcastle-Ottawa Scale (NOS). The NOS assesses research quality across three domains: Selection (up to 4 points), comparability (up to 2 points) and outcome assessment (up to 3 points). Each study received a total score ranging from 0 to 9, with a score of ≥7 indicating a high-quality study (16).

Statistical analysis. The hazard ratios (HRs) for PFS and OS, along with their corresponding 95% confidence intervals (CIs), as well as the CR rates, were extracted directly from the included studies. Heterogeneity among the studies was assessed using the Cochran Q test and the I^2 statistic. Since heterogeneity is always expected for the intervention effects among multiple studies from different groups and geographical locations, a random effects model was used to account for this. Publication bias was evaluated using a funnel plot. All statistical analyses were performed using Review Manager 5.4 (The Cochrane Collaboration), and $P<0.05$ was considered to indicate a statistically significant difference (17).

Results

Characteristics of the included studies. Following a comprehensive full-text screening, 8 articles were identified that initially met the inclusion criteria for analysis. However, 2 of these articles, authored by Sonneveld *et al* (12) and Smetana *et al* (11), were excluded as they did not provide HRs for PFS or OS. Consequently, the final analysis included 6 studies involving a total of 1,575 patients, as illustrated in Fig. 1. These studies were published between 2010 and 2022, with 1 study published in 2011 (14), 2 in 2019 (18,19), 1 in 2020 (20) and 2 in 2022 (21,22). The research was conducted across various countries, including China, Canada and the United States. The objective of these studies was to investigate the prognostic value of 1q21+ in patients with MM treated with bortezomib-based regimens. This was assessed by comparing PFS, OS and the response rates between patients with 1q21+ and those without. Among the 6 studies, 5 identified the presence of 1q21 when patients were newly diagnosed with MM, except the study by Chang *et al* (14). The study conducted by Chang *et al* (14) identified the chromosome aberrations at the relapsed stage of the disease prior to bortezomib therapy. The examination of the presence of 1q21+ was performed before the patients received bortezomib-based treatment in all studies. The observation periods of all studies were sufficient to calculate the PFS rate both in patients with 1q21+ and those without 1q21+ and were sufficient to calculate the OS rate in patients with 1q21+. The OS of patients without 1q21+ was not reached in the studies by Li *et al* (18) and Du *et al* (20).

The quality of the included studies was assessed using the NOS, with scores ranging from 7 to 8, indicating high quality. Among the included studies, 5 studies, comprising a total of 1,240 patients (with individual study sample sizes ranging from 85 to 414), reported PFS rates, along with the HR for PFS and the corresponding 95% CI (14,18,19,20,21). Additionally, 4 studies, involving 1,031 patients (with sample sizes ranging from 85 to 414), examined OS, HR for OS and 95% CI for HR (14,18,20,22). Furthermore, 3 studies, including 1,031 patients (with sample sizes ranging from 250 to 414), reported on the CR rate (18,20,22). A summary of the main characteristics of the included studies is detailed in Table I.

Meta-analysis results

Association between 1q21+ and the PFS rate of patients with MM. The findings of the meta-analysis revealed that the presence of 1q21+ was a detrimental prognostic factor for PFS in patients with MM undergoing bortezomib treatment (HR, 1.72; 95% CI, 1.53-1.93; $P<0.00001$). Notably, there was no observed heterogeneity among the included studies ($P=0.41$, $I^2=0\%$) (Fig. 2).

Association between 1q21+ and the OS rate of patients with MM. Similarly, the analysis of the OS demonstrated that 1q21+ was an unfavorable prognostic factor for patients with MM receiving bortezomib treatment (HR, 1.95; 95% CI, 1.58-2.42; $P<0.00001$). Notably, no significant heterogeneity was detected among the studies ($P=0.72$, $I^2=0\%$) (Fig. 3).

Association between 1q21+ and the CR rate of patients with MM. By contrast, the meta-analysis revealed that the presence of 1q21+ acted as a protective factor for the CR rate in patients with MM treated with bortezomib (OR, 0.64; 95% CI, 0.49-0.83; $P=0.0008$). However, no heterogeneity was observed among the studies ($P=0.39$, $I^2=0\%$) (Fig. 4).

Publication bias. No evidence of publication bias was detected in the analyses of OS, PFS and CR rate (Fig. 5).

Sensitivity analysis of PFS and OS. The sensitivity analysis for PFS included 4 studies. When any single study was excluded from the analysis, the combined results of the remaining studies consistently aligned with the original pooled estimates, indicating the robustness of the findings. Similarly, the sensitivity analysis for OS, which included 3 studies, showed that excluding any individual study did not alter the overall results, further confirming the stability of the study findings (Fig. 6).

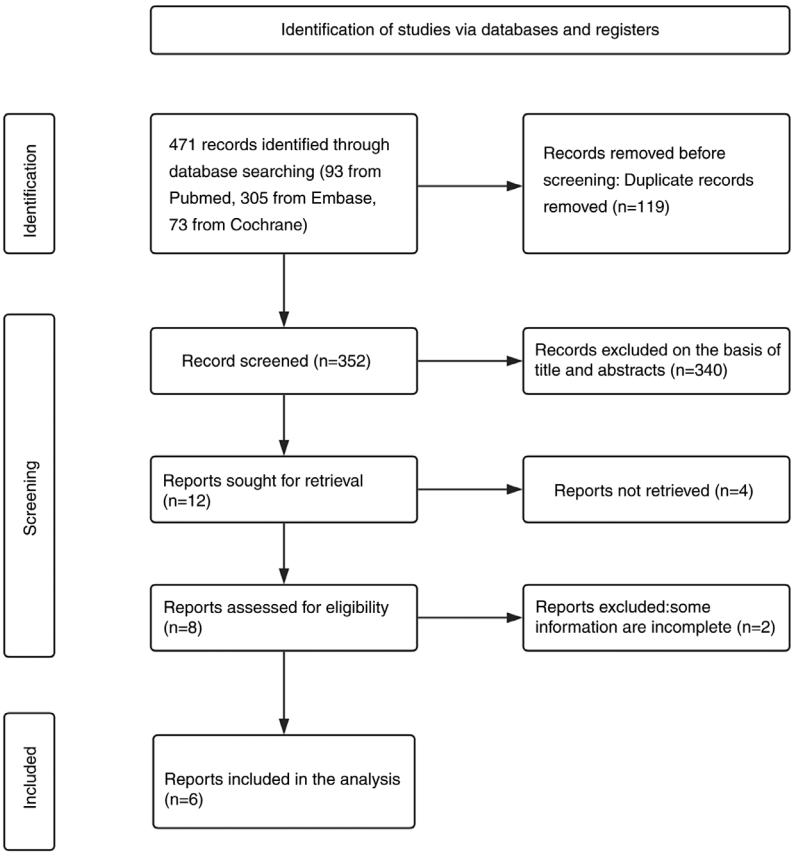

Figure 1. Flow chart of the study selection.

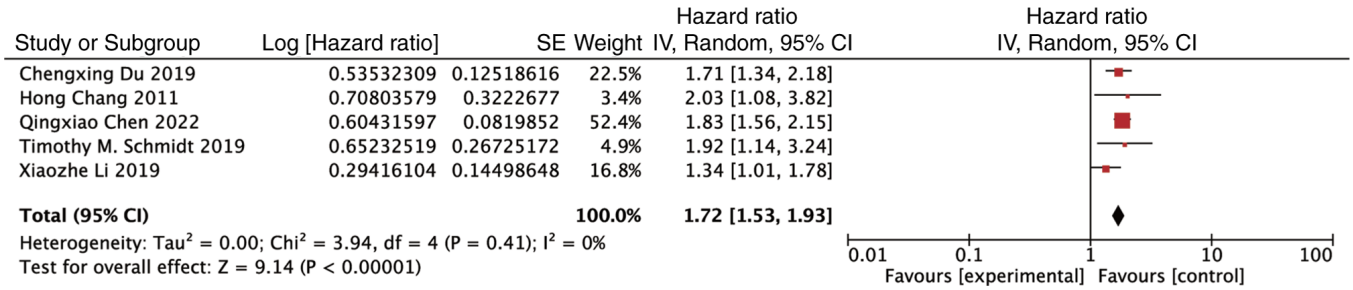

Figure 2. Forest plots showing the progression-free survival results for 1q21+ in patients with multiple myeloma treated with bortezomib. CI, confidence interval; SE, standard error.

Discussion

In total, ~40% of patients with MM exhibit 1q21+, a genetic aberration associated with poor prognosis (23). Over the past decades, the introduction of novel therapeutics has notably improved outcomes for patients with MM (24). Despite these advancements, the prognosis for patients with 1q21+ remains a significant challenge (25). Some studies suggest that, with appropriate treatment strategies, patients harboring certain high-risk factors can achieve survival outcomes comparable to those with standard risk. For instance, a large trial demonstrated that a treatment regimen comprising bortezomib-based induction, early autologous stem cell transplantation and bortezomib maintenance resulted in a median OS time of ~8 years (with an 8-year survival rate of 52%) for patients with del(17p), matching the survival rates of patients with standard-risk MM (26). In the HOVON-65/GMMG-HD4 trial, patients were randomized to receive either three cycles of VAD (arm A: vincristine, adriamycin and dexamethasone) or PAD (arm B: bortezomib, adriamycin and dexamethasone). With a median follow-up time of 40.3 months, the trial revealed that patients with 1q21+ experienced significantly improved OS rates when treated with bortezomib (3-year OS rates: Arm A, 59%, arm B, 83%; P=0.016) (10). Given these findings, it is imperative to explore whether bortezomib-based treatments can mitigate the adverse prognostic impact of 1q21+, thereby enabling patients with this genetic aberration to achieve survival outcomes comparable to those without the gain.

According to a study by Smetana *et al* (11), there was no significant difference in the overall response rate between patients with or without 1q21+ when treated with a bortezomib-based regimen (44.8 vs. 44.4%; P=0.996). Additionally,

Table I. Characteristics of the included studies.

Author, year	Country	Design	Sample size, n	Sex, % of males	Median β2M (range), mg/l	Median LDH (range), units/l	1q21+ positive, n	1q21+ negative, n	Outcomes	Median follow-up (range), months	Treatment	NOS	(Refs.)
Chang *et al*, 2011	Canada	Retro	85	61	2.4 0.4-19.9)	/	31	54	OS and PFS	37	VTD, VCD, VRD, VMP, PAD and VD	8	(14)
Li *et al*, 2019	China	Retro	414	58	/	172.0 (70.0-1356.0)	156	258	CR rate	23.8 (0.5-129.5)	Bortezomib-based	7	(18)
Schmidt *et al*, 2019	America	Retro	201	57	2.95	150	94	107	PFS	48	VRD	8	(19)
Du *et al*, 2020	China	Retro	367	/	/	/	203	164	OS, PFS and CR rate	43 (3-113)	VAD and VCD	7	(20)
Chen *et al*, 2022	China	Retro	258	57	3.90 (1.03-40.1)	185 (79-5758)	127	131	PFS	24.1 (1.1-71.0)	VD	7	(21)
Tang *et al*, 2022	China	Retro	250	55	/	/	167	83	OS and CR rate	/	VTD	7	(22)

β2M, β_2 microglobulin; CR, complete response; LDH, lactate dehydrogenase; OS, overall survival; PFS, progression-free survival; PAD, bortezomib combined with doxorubicin and dexamethasone; VTD, bortezomib combined with thalidomide and dexamethasone; VCD, bortezomib combined with cyclophosphamide and dexamethasone; VRD, bortezomib combined with lenalidomide and dexamethasone; VMP, bortezomib combined with melphalan and dexamethasone; VD, bortezomib combined with dexamethasone.

the differences in time to progression (TTP) and OS between the two groups were not statistically significant (TTP, 12.9 vs. 13.9 months; P=0.983; and OS, 29 vs. 37.1 months; P=0.146). Based on these findings, the study suggested that 1q21+ might not serve as an unfavorable prognostic factor in patients undergoing bortezomib treatment (11). However, a conflicting report by Du *et al* (20) indicated that patients with 1q21+ had a significantly shorter median PFS and OS time compared with those without the gain in a bortezomib-based cohort. Given these contradictory findings, a meta-analysis was conducted in the present study, including 6 studies and a total of 1,575 patients, to clarify the prognostic significance of 1q21+ in this context.

The results of the present study indicated that patients with 1q21+ were more likely to achieve a CR than those without it when undergoing bortezomib-based treatment (OR, 0.64; 95% CI, 0.49-0.83; P=0.0008). However, it is important to note that 1q21+ still conferred a poor prognostic outcome following bortezomib treatment, as evidenced by the PFS (HR, 1.81; 95% CI, 1.59-2.06; P<0.00001) and OS (HR, 2.06; 95% CI, 1.60-2.66; P<0.00001) results. Notably, no publication bias was identified, underscoring the reliability of these findings and providing valuable guidance for clinicians when selecting treatment strategies for patients with high-risk MM. Given the limited efficacy of bortezomib in improving outcomes for patients with 1q21+, we recommend that clinicians consider alternative treatment regimens for these individuals.

In the present study, the paradoxical results indicated that a higher percentage of patients with 1q21+ achieved CR but with a poor prognosis. The poor prognosis of patients with 1q21+ can be attributed to findings from the Total Therapy 3 trial. Specifically, it has been proposed that this poor efficacy is linked to the upregulation of proteasome 26S subunit ubiquitin receptor, non-ATPase 4 (PSMD4), a proteasome subunit encoded at 1q21. Notably, PSMD4 showed a strong correlation with the copy number of 1q and emerged as a significant poor prognostic factor in both the GEP-70 and GEP-80 models developed by the UAMS-MIRT group. The upregulation of PSMD4 appears to contribute to resistance against bortezomib, and the presence of additional copies of 1q21 further intensifies this resistance (27). There have been no relevant fundamental studies to determine why patients with 1q21+ are more likely to achieve CR than patients without 1q21+. We speculate that myeloma cells with 1q21+ may have a higher proteasome activity, with which bortezomib-based treatment can exert greater efficacy at first; therefore, a higher percentage of patients with MM harboring 1q21+ achieve CR with bortezomib-based regimens. However, as the disease develops, patients are highly susceptible to drug resistance, so even after achieving a CR after initial treatment, these patients will relapse early and eventually have a poor prognosis. Additionally, Cao *et al* (28) hypothesized that ageing of bone marrow mesenchymal stem cells is associated with the progression of MM. In the study, a prognostic risk model was established based on this assumption, in which a copy number of 1q21 >2 had a higher risk score and was associated with early progression (28). These findings provide support for considering 1q21+ as a high-risk factor, even for patients receiving bortezomib. However, more studies are needed to explain why 1q21+ is associated with achieving a CR.

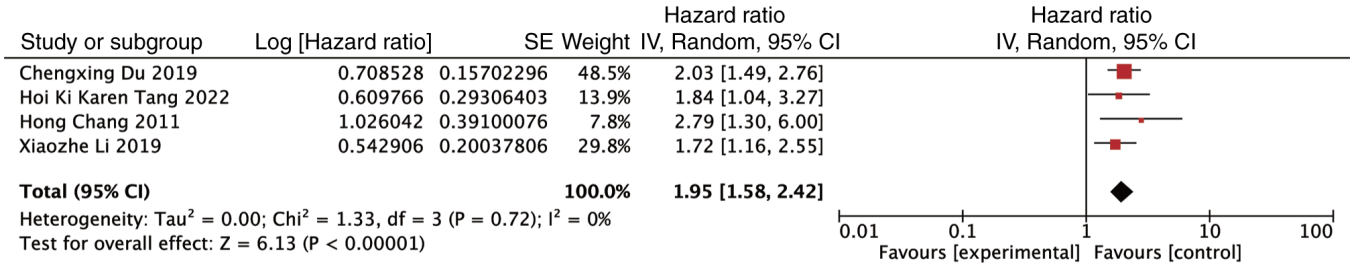

Figure 3. Forest plots showing the overall survival results for 1q21+ in patients with multiple myeloma treated with bortezomib. CI, confidence interval; SE, standard error.

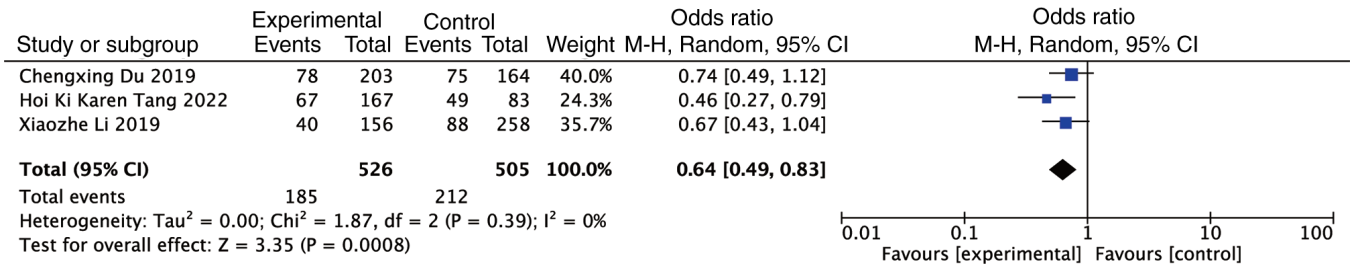

Figure 4. Forest plots showing the complete response results for 1q21+ in patients with multiple myeloma treated with bortezomib. CI, confidence interval.

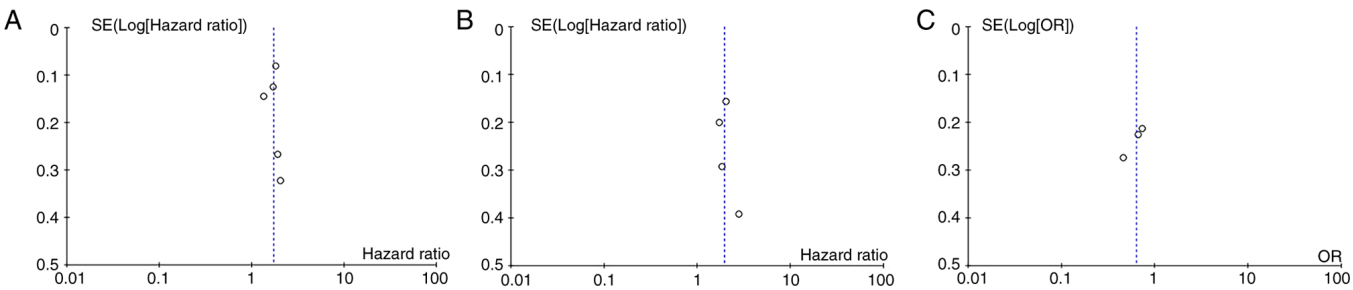

Figure 5. Funnel plots showing the publication bias for the (A) progression-free survival, (B) overall survival and (C) complete response results for 1q21+ in patients with multiple myeloma treated with bortezomib. SE, standard error; OR, odds ratio.

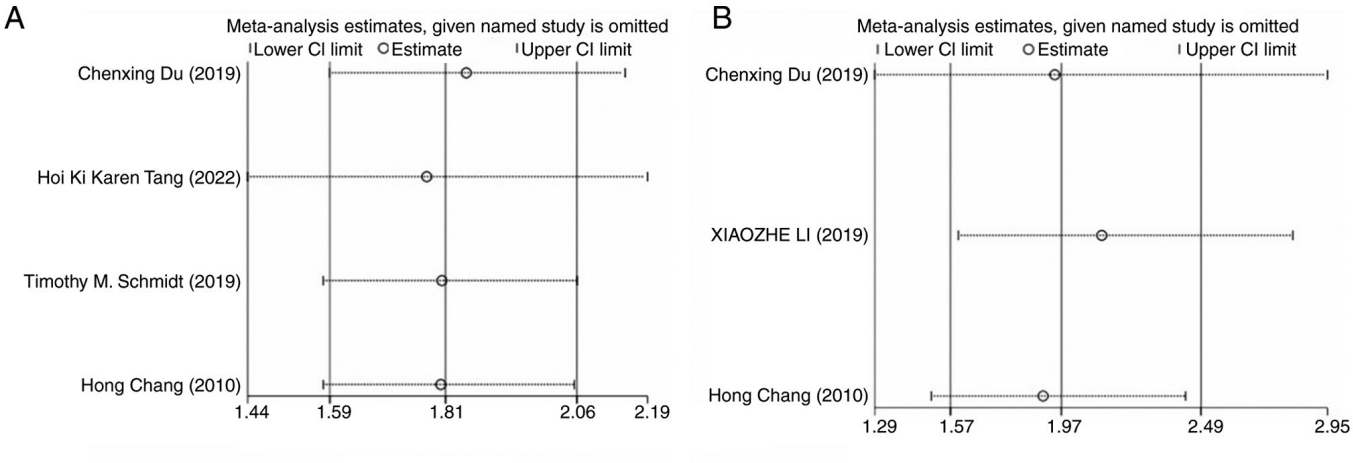

Figure 6. Sensitivity analysis of the studies reporting (A) progression-free survival and (B) overall survival. CI, confidence interval.

Generally, 1q21 refers to the presence of additional copies of the 21 portions of chromosome 1q (29). The number of these copies can significantly impact the prognostic significance of 1q21+, with an increased copy number often associated with worse outcomes (13,25,30). According to a study by Gao *et al* (31), 1q21+ becomes an unfavorable prognostic factor when ≥4 copies

are present. Additionally, while bortezomib-based treatment may improve PFS in patients with 3 copies, it appears less effective in those with ≥4 copies (31). Unfortunately, due to the limited number of studies in this area, it was not possible to conduct a subgroup analysis based on varying copy numbers of 1q21. Future research should focus on examining the prognostic value of different 1q21 copy numbers under treatment with novel therapeutic agents.

The present study specifically investigated the impact of bortezomib on patients with 1q21+. However, further research is needed to explore the effectiveness of other novel therapies, such as immunomodulatory drugs and anti-CD38 monoclonal antibodies, in patients with MM harboring 1q21+. Such studies will be crucial in identifying the most appropriate treatment strategies for these patients. Several limitations of the present study must be acknowledged. First, most of the included studies were retrospective in nature, which is a significant limitation. Second, the geographic scope of the included studies was predominantly confined to three countries, which may introduce some bias. Lastly, there is variability in the treatment strategies employed across the different studies, which could potentially influence the results.

Additionally, several strengths of the present study should be highlighted. First, a large sample size of 1,575 patients was included in the analysis, allowing for a robust quantitative assessment of the prognostic significance of 1q21+. This comprehensive analysis offered a powerful evaluation of this important issue. Second, the present study incorporated 5 studies published between 2019 and 2022, ensuring the timeliness and relevance of the findings. Lastly, the analysis was not impacted by publication bias, further strengthening the reliability of the conclusions.

In conclusion, the results of the present study, based on 6 studies involving 1,575 patients diagnosed with MM, consistently demonstrated that 1q21+ remains a significant high-risk factor among patients with MM treated with bortezomib. Although patients with MM harboring 1q21+ may exhibit a higher likelihood of achieving CR under bortezomib treatment compared with those without this aberration, it is clear that bortezomib cannot fully mitigate the adverse prognostic impact associated with 1q21+. Therefore, clinicians are encouraged to consider alternative treatment strategies for patients with MM harboring 1q21+ aberration.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

XZ and SL confirm the authenticity of all the raw data. XZ contributed to the conception and design of the study, data analysis and interpretation, as well as manuscript writing. SL contributed to manuscript writing and data analysis and interpretation. KL contributed to data analysis and interpretation. JH and TL contributed to the design of the study, submission and communication. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Siegel RL, Miller KD, Fuchs HE and Jemal A: Cancer statistics, 2021. CA Cancer J Clin 71: 7-33, 2021.
2. Pulte D, Jansen L, Castro FA, Emrich K, Katalinic A, Holleczek B and Brenner H; GEKID Cancer Survival Working Group: Trends in survival of multiple myeloma patients in Germany and the United States in the first decade of the 21st century. Br J Haematol 171: 189-196, 2015.
3. Cullis J: Haematology: Multiple myeloma. Clin Med (Lond) 19: 188, 2019.
4. Sonneveld P, Avet-Loiseau H, Lonial S, Usmani S, Siegel D, Anderson KC, Chng WJ, Moreau P, Attal M, Kyle RA, *et al*: Treatment of multiple myeloma with high-risk cytogenetics: A consensus of the International Myeloma Working Group. Blood 127: 2955-2962, 2016.
5. Soekojo CY and Chng WJ: Treatment horizon in multiple myeloma. Eur J Haematol 109: 425-440, 2022.
6. Burroughs Garcìa J, Eufemiese RA, Storti P, Sammarelli G, Craviotto L, Todaro G, Toscani D, Marchica V and Giuliani N: Role of 1q21 in multiple myeloma: From pathogenesis to possible therapeutic targets. Cells 10: 1360, 2021.
7. Hanamura I: Multiple myeloma with High-risk cytogenetics and its treatment approach. Int J Hematol 115: 762-777, 2022.
8. D'Agostino M, Cairns DA, Lahuerta JJ, Wester R, Bertsch U, Waage A, Zamagni E, Mateos MV, Dall'Olio D, van de Donk NWCJ, *et al*: Second revision of the international staging system (R2-ISS) for overall survival in multiple myeloma: A european myeloma network (EMN) report within the HARMONY project. J Clin Oncol 40: 3406-3418, 2022.
9. Hassan H and Szalat R: Genetic predictors of mortality in patients with multiple myeloma. Appl Clin Genet 14: 241-254, 2021.
10. McBride A and Ryan PY: Proteasome inhibitors in the treatment of multiple myeloma. Expert Rev Anticancer Ther 13: 339-538, 2013.
11. Smetana J, Berankova K, Zaoralova R, Nemec P, Greslikova H, Kupska R, Mikulasova A, Frohlich J, Sevcikova S, Zahradova L, *et al*: Gain(1)(q21) is an unfavorable genetic prognostic factor for patients with relapsed multiple myeloma treated with thalidomide but not for those treated with bortezomib. Clin Lymphoma Myeloma Leuk 13: 123-130, 2013.
12. Sonneveld P, Schmidt-Wolf IG, van der Holt B, El Jarari L, Bertsch U, Salwender H, Zweegman S, Vellenga E, Broyl A, Blau IW, *et al*: Bortezomib induction and maintenance treatment in patients with newly diagnosed multiple myeloma: Results of the randomized phase III HOVON-65/GMMG-HD4 trial. J Clin Oncol 30: 2946-2955, 2012.
13. An G, Xu Y, Shi L, Shizhen Z, Deng S, Xie Z, Sui W, Zhan F and Qiu L: Chromosome 1q21 gains confer inferior outcomes in multiple myeloma treated with bortezomib but copy number variation and percentage of plasma cells involved have no additional prognostic value. Haematologica 99: 353-359, 2014.
14. Chang H, Trieu Y, Qi X, Jiang NN, Xu W and Reece D: Impact of cytogenetics in patients with relapsed or refractory multiple myeloma treated with bortezomib: Adverse effect of 1q21 gains. Leuk Res 35: 95-98, 2011.

15. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J and Moher D: The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: Explanation and elaboration. BMJ 339: b2700, 2009.
16. Wells GA, Shea BJ, O'Connell D, Peterson J and Tugwell P: The Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomized studies in meta-analysis. Sci Educ, 2000.
17. Lee YH: An overview of meta-analysis for clinicians. Korean J Intern Med 33: 277-283, 2018.
18. Li X, Chen W, Wu Y, Li J, Chen L, Fang B, Feng Y, Liu J, Chen M, Gu J, *et al*: 1q21 Gain Combined with High-risk factors is a heterogeneous prognostic factor in newly diagnosed multiple myeloma: A multicenter study in China. Oncologist 24: e1132-e1140, 2019.
19. Schmidt TM, Barwick BG, Joseph N, Heffner LT, Hofmeister CC, Bernal L, Dhodapkar MV, Gupta VA, Jaye DL, Wu J, *et al*: Gain of Chromosome 1q is associated with early progression in multiple myeloma patients treated with lenalidomide, bortezomib, and dexamethasone. Blood Cancer J 9: 94, 2019.
20. Du C, Mao X, Xu Y, Yan Y, Yuan C, Du X, Liu J, Fan H, Wang Q, Sui W, *et al*: 1q21 gain but not t(4;14) indicates inferior outcomes in multiple myeloma treated with bortezomib. Leuk Lymphoma 61: 1201-1210, 2020.
21. Chen Q, Han X, Zheng G, Yang Y, Li Y, Zhang E, Yang L, Dong M, He D, He J and Cai Z: The adverse impact of a gain in chromosome 1q on the prognosis of multiple myeloma treated with bortezomib-based regimens: A retrospective single-center study in China. Front Oncol 12: 1084683, 2022.
22. Tang HKK, Fung CY, Morgan GJ, Kumar S, Siu L, Ip HWA, Yip SF, Lau KNH, Lau CK, Lee H, *et al*: The impact of bortezomib-based induction in newly diagnosed multiple myeloma with chromosome 1q21 gain. Ther Adv Hematol 13: 20406207221082043, 2022.
23. Bisht K, Walker B, Kumar SK, Spicka I, Moreau P, Martin T, Costa LJ, Richter J, Fukao T, Macé S, *et al*: Chromosomal 1q21 abnormalities in multiple myeloma: A review of translational, clinical research, and therapeutic strategies. Expert Rev Hematol 14: 1099-1114, 2021.
24. Kumar SK, Dispenzieri A, Lacy MQ, Gertz MA, Buadi FK, Pandey S, Kapoor P, Dingli D, Hayman SR, Leung N, *et al*: Continued improvement in survival in multiple myeloma: Changes in early mortality and outcomes in older patients. Leukemia 28: 1122-1128, 2014.
25. Schmidt TM, Fonseca R and Usmani SZ: Chromosome 1q21 abnormalities in multiple myeloma. Blood Cancer J 11: 83, 2021.
26. Rajkumar SV: Multiple myeloma: 2022 update on diagnosis, risk stratification, and management. Am J Hematol 97: 1086-1107, 2022.
27. Shaughnessy JD Jr, Qu P, Usmani S, Heuck CJ, Zhang Q, Zhou Y, Tian E, Hanamura I, van Rhee F, Anaissie E, *et al*: Pharmacogenomics of bortezomib test-dosing identifies hyper-expression of proteasome genes, especially PSMD4, as novel high-risk feature in myeloma treated with Total Therapy 3. Blood 118: 3512-3524, 2011.
28. Cao YJ, Zheng YH, Li Q, Zheng J, Ma LT, Zhao CJ and Li T: MSC Senescence-related genes are associated with myeloma prognosis and lipid metabolism-mediated resistance to proteasome inhibitors. J Oncol 2022: 4705654, 2022.
29. Walker BA, Mavrommatis K, Wardell CP, Ashby TC, Bauer M, Davies F, Rosenthal A, Wang H, Qu P, Hoering A, *et al*: A high-risk, Double-Hit, group of newly diagnosed myeloma identified by genomic analysis. Leukemia 33: 159-170, 2019.
30. Neben K, Lokhorst HM, Jauch A, Bertsch U, Hielscher T, van der Holt B, Salwender H, Blau IW, Weisel K, Pfreundschuh M, *et al*: Administration of bortezomib before and after autologous stem cell transplantation improves outcome in multiple myeloma patients with deletion 17p. Blood 119: 940-948, 2012.
31. Gao L, Liu Y, Li Y, Feng L, Wang Z, Wen L, Wang F, Huang X, Lu J and Lai Y: The Importance of FISH Signal Cut-off value and copy number variation for 1q21 in newly diagnosed multiple myeloma: Is it underestimated? Clin Lymphoma Myeloma Leuk 22: 535-544, 2022.