Postprint: Survival Analysis of Bortezomib-Based Regimens in Newly Diagnosed Very Elderly Patients with Multiple Myeloma

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Abstract

Background Multiple myeloma (MM) is a highly heterogeneous disease. Ultra-elderly MM patients constitute a special population for whom treatment decisions and general evaluation lack sufficient evidence-based support, and frailty assessment remains controversial, warranting further investigation.

Objective To investigate the general clinical characteristics and prognostic factors for survival in Chinese ultra-elderly newly treated MM patients receiving bortezomib-based regimens, and to evaluate the optimal assessment model for general condition in ultra-elderly MM patients.

Methods We retrospectively analyzed data from 29 ultra-elderly newly diagnosed MM patients admitted to the Shijingshan Campus of Beijing Chaoyang Hospital between November 2013 and January 2023. Survival follow-up was conducted through the hospital's medical record system until April 1, 2023. The study endpoints were overall survival (OS) and progression-free survival (PFS). Patients were stratified into a two-drug regimen group (n=18) and a three-drug regimen group (n=11) based on treatment protocol, and clinical and genetic characteristics were compared between groups. Frailty status was assessed using the Geriatric Assessment (GA) score, Myeloma Research Alliance Risk Profile (MRP) score, and Mayo score. Treatment response was evaluated accordingly. Kaplan-Meier method was used to generate survival curves for OS and PFS. Univariate analysis of factors influencing OS and PFS was performed using the Log-rank test, and multivariate Cox proportional hazards regression model was employed to identify independent prognostic factors.

Results The median PFS was 8.70 months (range 1.90–43.87 months), and the median OS was 17.23 months (range 2.00–72.83 months). At the final follow-up, 21 patients (72.41%) had experienced disease progression (PD) or relapse,

and 12 patients (41.38%) had died. The objective response rate (ORR) to first-line therapy was 82.76% (24/29), with a partial response (PR) rate of 51.72% (15/29), a very good partial response (VGPR) rate of 24.14% (7/29), and a complete response (CR) rate of 6.90% (2/29). No statistically significant differences were observed in CR rate, VGPR rate, PR rate, or ORR between the two treatment groups (P>0.05). Multivariate Cox proportional hazards regression analysis revealed that MRP-defined frailty (HR=0.213, 95%CI=0.049–0.924, P=0.039), elevated serum corrected calcium (HR=0.153, 95%CI=0.041–0.570, P=0.005), and maintenance therapy (HR=4.301, 95%CI=1.219–15.169, P=0.023) were independent prognostic factors for PFS. Maintenance therapy (HR=4.372, 95%CI=1.049–18.221, P=0.043) was also identified as an independent prognostic factor for OS.

Conclusion No significant differences in efficacy or prognosis were observed between two-drug and three-drug bortezomib-containing regimens for ultra-elderly newly treated MM patients. Elevated serum corrected calcium and maintenance therapy were independent prognostic factors for survival. The MRP score may be used to evaluate prognosis in ultra-elderly newly treated MM patients.

Full Text

Survival and Prognosis Analysis of Bortezomib-Based Regimens in Newly Diagnosed Super-Aged Multiple Myeloma Patients

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Abstract

Background: Multiple myeloma (MM) is a highly heterogeneous disease, and super-aged patients with MM represent a special population. Treatment decisions and general evaluation for these patients lack evidence-based medical support, and there is controversy regarding frailty assessment, necessitating further research.

Objective: To explore the clinical characteristics and prognostic factors affecting survival in newly diagnosed super-aged MM patients in China treated with bortezomib-based regimens, and to evaluate the optimal assessment model for general condition in this patient population.

Methods: We retrospectively analyzed clinical data from 29 newly diagnosed super-aged MM patients admitted to the Shijingshan Campus of Beijing Chao-

Yang Hospital between November 2013 and January 2023. Survival follow-up was conducted through the hospital's medical record system until April 1, 2023. The study endpoints were overall survival (OS) and progression-free survival (PFS). Patients were divided into a two-drug treatment group (n=18) and a three-drug treatment group (n=11), and their clinical and genetic characteristics were compared. Frailty status was evaluated using the Geriatric Assessment (GA) score, UK Myeloma Research Alliance Risk Profile (MRP) score, and Mayo score. Treatment efficacy was assessed accordingly. Kaplan-Meier method was used to plot survival curves for OS and PFS. Log-rank test was employed for univariate analysis of OS and PFS influencing factors, and multivariate Cox proportional hazards regression model was used to analyze independent prognostic factors.

Results: The median PFS was 8.70 months (range: 1.90-43.87 months), and the median OS was 17.23 months (range: 2.00-72.83 months). By the final follow-up, 21 patients (72.41%) had experienced disease progression (PD) or relapse, and 12 patients (41.38%) had died. The objective response rate (ORR) for first-line treatment was 82.76% (24/29), with a partial response (PR) rate of 51.72% (15/29), very good partial response (VGPR) rate of 24.14% (7/29), and complete response (CR) rate of 6.90% (2/29). There were no statistically significant differences in CR, VGPR, PR, or ORR rates between the two treatment groups (P>0.05). Multivariate Cox regression analysis revealed that MRP-defined frailty (HR=0.213, 95%CI=0.049-0.924, P=0.039), elevated serum corrected calcium (HR=0.153, 95%CI=0.041-0.570, P=0.005), and maintenance therapy (HR=4.301, 95%CI=1.219-15.169, P=0.023) were independent prognostic factors for PFS. Maintenance therapy (HR=4.372, 95%CI=1.049-18.221, P=0.043) was an independent prognostic factor for OS.

Conclusion: There was no significant difference in efficacy and prognosis between two-drug and three-drug bortezomib-based regimens for newly diagnosed super-aged MM patients. Elevated serum corrected calcium and maintenance therapy were independent prognostic factors for survival. The MRP score can be used to assess prognosis in newly diagnosed super-aged MM patients.

Keywords: Multiple myeloma; Bortezomib; Prognosis; Frailty; Aged, 80 and over; Overall survival; Progression-free survival

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Multiple myeloma (MM) originates from monoclonal gammopathy of undetermined significance (MGUS) and predominantly occurs in middle-aged and elderly individuals, accounting for approximately 10% of hematologic malignancies and ranking as the second most common hematologic cancer [1]. MM is a malignant proliferative disease of plasma cells that affects 3%-5% of individuals over 65 years and 10% of those over 80 years. MGUS progresses to active MM at a rate of 1%-2% per year, with an 18% risk of progression within 20 years [2]. However, most clinical trials have excluded super-aged MM patients, resulting in a relative lack of evidence-based medical guidance for treatment selection and

prognostic risk assessment in this population. The International Myeloma Working Group (IMWG) proposed the Geriatric Assessment (GA) system in 2015 to evaluate the comprehensive status of elderly cancer patients. Currently, GA is the most commonly used scoring system for assessing elderly MM patients, but it has limitations, particularly regarding subjectivity in scoring and the absolute use of age as a criterion. Directly classifying all patients over 80 as frail may be inappropriate under certain conditions. To overcome these limitations, the UK Myeloma Research Alliance proposed the UK Myeloma Research Alliance Risk Profile (MRP) score, in addition to the more convenient Mayo score. This study aims to retrospectively analyze the clinical characteristics and compare the impact of two-drug versus three-drug bortezomib-based regimens on survival prognosis in newly diagnosed super-aged MM patients in China, while exploring the optimal general condition assessment model for this population to provide evidence for individualized treatment.

1.1 Study Subjects

We retrospectively collected clinical data from newly diagnosed super-aged MM patients admitted to the Shijingshan Campus of Beijing Chao-Yang Hospital between November 2013 and January 2023. Inclusion criteria were: (1) diagnosis met the criteria of the "Chinese Guidelines for the Diagnosis and Treatment of Multiple Myeloma" [3]; (2) age $\geq$ 80 years; (3) first-line treatment with bortezomib-containing two-drug or three-drug regimens at a dose intensity of at least 70% of the standard dose; and (4) complete baseline clinical data and follow-up information. Exclusion criteria were: (1) concurrent uncontrolled malignancies; and (2) prior anti-MM drug use before bortezomib treatment. Based on treatment regimen selection, patients were divided into a two-drug treatment group (n=18) and a three-drug treatment group (n=11).

1.2 Treatment Regimens

The two-drug treatment group received the VD regimen (bortezomib 1.3 mg/m^2 on days 1, 4, 8, and 11; dexamethasone 20-40 mg on days 1, 4, 8, and 11). The three-drug treatment group received either VTD (bortezomib 1.3 mg/m^2 on days 1, 4, 8, and 11; thalidomide 100-200 mg on days 1-21; dexamethasone 20-40 mg on days 1, 4, 8, and 11), VCD (bortezomib 1.3 mg/m^2 on days 1, 4, 8, and 11; cyclophosphamide 200-300 mg/m^2 on days 1-4; dexamethasone 20-40 mg on days 1, 4, 8, and 11), or VRD (bortezomib 1.3 mg/m^2 on days 1, 4, 8, and 11; lenalidomide 25 mg every other day on days 1-21; dexamethasone 20-40 mg on days 1, 4, 8, and 11). For patients experiencing severe peripheral neuropathy or intolerance, the regimen could be adjusted to weekly bortezomib administration. Maintenance therapy could include lenalidomide 25 mg every other day on days 1-21, thalidomide 100-200 mg daily, or bortezomib 1.3 mg/m^2 once every two weeks [3]. None of the patients received autologous hematopoietic stem cell transplantation.

1.3 General Data Collection

We collected all clinical and genetic factors that might affect survival and prognosis in MM patients, including: sex, GA score, MRP score, Mayo score, hemoglobin, platelet count, white blood cell count, erythrocyte sedimentation rate (ESR), serum corrected calcium, creatinine, triglycerides, cholesterol, deep vein thrombosis, bone pain, extramedullary disease, 1q21 amplification, Durie-Salmon (DS) stage, revised international staging system (R-ISS) stage, treatment regimen, infection during treatment, and maintenance therapy.

1.4.1 GA Score The GA score comprises four indicators: age, Activities of Daily Living (ADL), Instrumental Activities of Daily Living (IADL), and Charlson Comorbidity Index (CCI) [4-5]. Based on the total score, patients were classified as fit (0 points), intermediate fitness (1 point), or frail ($ $2 points) [6], with fit and intermediate fitness combined as non-frail.

1.4.2 MRP Score The MRP score includes four objective factors: Eastern Cooperative Oncology Group (ECOG) performance status, age, International Staging System (ISS), and C-reactive protein (CRP) [7-9]. The calculation formula is: MRP score = (ECOG-PS score - 2) × 0.199 + (age - 74.7) × 0.0165 + (ISS stage - 2) × 0.212 + [log(CRP + 1) - 2.08] × 0.0315. Patients were categorized as fit (MRP score < -0.256), intermediate fitness (-0.256 ≤ MRP score ≤ -0.028), or frail (MRP score > -0.028) [7], with fit and intermediate fitness combined as non-frail.

1.4.3 Mayo Score The Mayo score includes age ≥ 70 years, ECOG performance status, and serum N-terminal prohormone of brain natriuretic peptide (NT-proBNP) ≥ 300 ng/L [10-11], with each variable assigned 1 point. Patients were classified as fit (0 points), intermediate fitness (1-2 points), or frail (3 points) [10], with fit and intermediate fitness combined as non-frail.

1.5 Efficacy Evaluation

Treatment response was assessed according to the 2006 IMWG International Myeloma Uniform Response Criteria. This includes stringent complete response (sCR), complete response (CR), very good partial response (VGPR), partial response (PR), minimal response (MR), stable disease (SD), progressive disease (PD), clinical relapse, and relapse from CR. The objective response rate (ORR) was defined as the proportion of patients achieving ≥ PR, calculated as ORR = [(CR + VGPR + PR) / total sample size] × 100%. In addition to monitoring changes in M protein and free light chain levels, measurable extramedullary disease (EMD) at baseline was evaluated by sum of products of greatest diameters (SPD), with a ≥ 50% reduction considered PR and complete disappearance of EMD considered CR.

1.6 Follow-up

All patients were followed up through the Beijing Chao-Yang Hospital medical record system and via telephone contact with patients or their relatives until April 1, 2023. The study endpoints were overall survival (OS) and progression-free survival (PFS). OS was defined as the time from diagnosis to death from any cause or last follow-up, while PFS was defined as the time from diagnosis to disease progression, death, or last follow-up.

1.7 Statistical Methods

SPSS 25.0 statistical software was used for data analysis. Categorical data were expressed as percentages and compared between groups using chi-square test or Fisher's exact test. Survival analysis was performed using the Kaplan-Meier method to plot OS and PFS curves. Log-rank test was used for univariate analysis of factors influencing OS and PFS. Multivariate Cox proportional hazards regression model was used to analyze independent prognostic factors for OS and PFS. $P < 0.05$ was considered statistically significant.

2.1 General Patient Characteristics

Between November 2013 and January 2023, 38 MM patients aged $\geq$ 80 years were admitted to the Shijingshan Campus of Beijing Chao-Yang Hospital, of which 29 met the inclusion criteria and were included in the analysis. The cohort comprised 20 males (69.0%) and 9 females (31.0%), with a median age at onset of 84 years (range: 80-91 years). ISS staging showed stage I in 1 patient (3.4%), stage II in 10 patients (34.5%), and stage III in 18 patients (62.1%). R-ISS staging showed stage I in 10 patients (34.5%), stage II in 15 patients (51.7%), and stage III in 4 patients (13.8%). Fluorescence in situ hybridization (FISH) detected 1q21 amplification in 9 patients (31.0%), TP53 mutation in 1 patient (3.4%), IGH/FGFR3 (t[4,14]) translocation in 1 patient (3.4%), and IGH/CCND1 (t[11,14]) translocation in 5 patients (17.2%). Extramedullary disease (EMD) was present in 10 patients (34.5%). The two-drug treatment group included 18 patients (62.1%), all receiving VD regimen (bortezomib + dexamethasone). The three-drug treatment group included 11 patients (37.9%), comprising 1 patient receiving VTD (bortezomib + thalidomide + dexamethasone), 7 patients receiving VCD (bortezomib + cyclophosphamide + dexamethasone), and 3 patients receiving VRD (bortezomib + lenalidomide + dexamethasone).

2.2 Frailty Assessment in Newly Diagnosed Super-Aged MM Patients

GA scoring revealed that all 29 patients were classified as frail ($ $2 points), including 7 patients with 2 points, 6 with 3 points, 12 with 4 points, and 4 with 5 points. MRP scoring identified 18 patients as frail (MRP score > -0.028), 4 as intermediate fitness (-0.256 $\leq$ MRP score $\leq$ -0.028), and 7 as fit (MRP score < -0.256). Mayo scoring classified 16 patients as frail (3 points), 9 as intermediate fitness (1-2 points), and 4 as fit (0 points).

2.3 Comparison of Clinical Characteristics Between Groups

There were no statistically significant differences in clinical or genetic characteristics between the two-drug and three-drug treatment groups (P > 0.05) .

2.4 Survival and Treatment Efficacy

The median PFS was 8.70 months (range: 1.90-43.87 months) and median OS was 17.23 months (range: 2.00-72.83 months) [Figure 1: see original paper]A, 1B. By the final follow-up, 21 patients (72.41%) had experienced PD or relapse, and 12 patients (41.38%) had died. The ORR for first-line treatment was 82.76% (24/29), with a PR rate of 51.72% (15/29), VGPR rate of 24.14% (7/29), and CR rate of 6.90% (2/29). No significant differences were observed in CR, VGPR, PR, or ORR rates between the two treatment groups (P > 0.05) .

2.5 Univariate Analysis of Prognostic Factors

2.5.1 3-Year PFS Rate Univariate analysis showed no significant differences in 3-year PFS rates based on sex, Mayo score, hemoglobin, platelet count, white blood cell count, ESR, creatinine, triglycerides, cholesterol, deep vein thrombosis, bone pain, DS stage, extramedullary disease, 1q21 amplification, treatment regimen, or infection during treatment (P > 0.05). However, patients with GA score <3 points had higher 3-year PFS rates than those with GA score $ $3 points (P = 0.023). Non-frail patients by MRP score had higher 3-year PFS rates than frail patients (P = 0.002). Patients without elevated serum corrected calcium had higher 3-year PFS rates than those with elevated calcium (P = 0.001). Patients with R-ISS stage I-II had higher 3-year PFS rates than those with stage III (P = 0.019). Patients receiving maintenance therapy had higher 3-year PFS rates than those without maintenance therapy (P < 0.001) [Figure 2: see original paper]A-E.

2.5.2 3-Year OS Rate Univariate analysis showed no significant differences in 3-year OS rates based on sex, Mayo score, hemoglobin, platelet count, white blood cell count, ESR, creatinine, triglycerides, cholesterol, deep vein thrombosis, bone pain, DS stage, extramedullary disease, 1q21 amplification, R-ISS stage, treatment regimen, or infection during treatment (P > 0.05). However, patients with GA score <3 points had higher 3-year OS rates than those with GA score $ $3 points (P = 0.022). Non-frail patients by MRP score had higher 3-year OS rates than frail patients (P = 0.018). Patients without elevated serum corrected calcium had higher 3-year OS rates than those with elevated calcium (P = 0.017). Patients receiving maintenance therapy had higher 3-year OS rates than those without maintenance therapy (P = 0.002) [Figure 2: see original paper]F-I.

2.6 Multivariate Cox Proportional Hazards Regression Analysis

Using 3-year PFS and OS rates as dependent variables, we included factors with $P < 0.1$ in univariate analysis as independent variables: GA score ($ $3 points = 1, <3 points = 0), MRP score (frail = 1, non-frail = 0), serum corrected calcium (elevated = 1, not elevated = 0), R-ISS stage (stage III = 1, stages I-II = 0), maintenance therapy (yes = 1, no = 0), and DS stage (stage III = 2, stages I-II = 1). Multivariate analysis revealed that MRP-defined frailty, elevated serum corrected calcium, and maintenance therapy were independent prognostic factors for PFS ($P < 0.05$). Maintenance therapy was an independent prognostic factor for OS ($P < 0.05$) .

MM is a highly heterogeneous disease. In recent years, the availability of novel agents has improved quality of life for MM patients [12]. Prognostic evaluation of MM has incorporated cytogenetic and gene-related indicators [13-14], and real-world first-line treatment patterns for elderly MM in China have been reported [15]. However, patients over 80 years represent a unique group with varying physical performance status and treatment tolerance [16]. Previous studies have shown that with increasing age, the prognostic impact of cytogenetics decreases while patient-specific characteristics become more influential [17], highlighting the importance of clinical features in super-aged MM patients. Most clinical trials have excluded patients aged $ $80 years, leaving treatment decisions and prognostic evaluation for this population lacking evidence-based support. Frailty assessment remains controversial. The IMWG GA score, the first frailty assessment model applied to MM, combines age, ADL, IADL, and CCI to comprehensively reflect physical, functional, and social factors, and has been widely recommended in guidelines following multiple validations [18]. However, GA has limitations, including excessive subjectivity (two of four factors are subjective scores) and the absolute use of age, which may compromise consistency and inadequately represent the status of patients over 80 in modern society. The Mayo score, which includes only age $ $70 years, ECOG-PS, and NT-proBNP, is more convenient and objective, but variable NT-proBNP standards across centers limit its clinical application [19]. The MRP score, proposed by the UK Myeloma Research Alliance, is based on biochemical and hematological indicators, improving the efficiency and objectivity of risk stratification in elderly MM patients.

This study retrospectively analyzed clinical characteristics and prognostic factors in newly diagnosed super-aged MM patients treated with bortezomib-based regimens, comparing GA, MRP, and Mayo scoring systems. We found that high-risk cytogenetics, advanced DS stage, or R-ISS stage were not prognostic factors in patients $ $80 years, consistent with some previous studies [11]. A recent real-world study of elderly MM in China showed that 30% of responding patients did not initiate first-line maintenance therapy after induction, indicating inadequate treatment [20]. Our study reaffirmed the importance of maintenance therapy in elderly MM patients, identifying it as the only independent prognostic factor for OS in newly diagnosed super-aged MM. We also found that elevated

serum corrected calcium and lack of maintenance therapy were independent risk factors for shorter PFS. Multiple studies have demonstrated that frailty assessment is crucial in elderly patients, influencing both treatment selection and outcomes [21-23]. Our study further explored the correlation between three frailty assessment models and prognosis, suggesting that MRP score can predict PFS in super-aged MM patients, though none of the three models significantly impacted OS.

In summary, this study explored the clinical characteristics, survival outcomes, and prognostic factors in newly diagnosed super-aged MM patients $ $80 years, innovatively evaluating three frailty assessment models. We confirmed the importance of maintenance therapy in this population. While our findings have clinical practice implications, limitations include the small sample size, as epidemiological data from 2019 showed a median onset age of 69 years in China, resulting in fewer patients $ $80 years. Additionally, due to resource constraints, minimal residual disease (MRD) was not assessed [24], preventing further MRD-based efficacy evaluation in CR patients. In conclusion, elderly MM is a highly heterogeneous group requiring precision medicine. More accurate prognostic models are needed to guide safe, effective, and personalized therapy, maximizing survival opportunities and improving outcomes for super-aged MM patients.

Author Contributions: ZHAO Fengyi conceived the research idea on frailty scoring and prognosis in super-aged MM, designed the study, and performed data collation and statistical analysis. LI Xin, ZHAN Xiaokai, and ZHANG Jiajia implemented the study and created figures and tables. SHEN Man, TANG Ran, and FAN Sibin collected case data, conducted telephone follow-ups, and applied SPSS software. ZHAO Fengyi, LI Xin, ZHAN Xiaokai, ZHANG Jiajia, SHEN Man, TANG Ran, and FAN Sibin drafted the manuscript. HUANG Zhongxia revised the final manuscript, oversaw the overall research concept, and supervised the project.

Conflict of Interest: The authors declare no conflict of interest.

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Note: Figure translations are in progress. See original paper for figures.