Postprint: Efficacy and Safety of Carfilzomib for Multiple Myeloma

Authors: Zheng Boyue, Fu Jiyi, Wu Jiafei, Wang Jun, Li Hui, Li Hui

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Abstract

Background: Since its launch in China in 2022, carfilzomib has been widely used in patients with relapsed and refractory multiple myeloma (RRMM); however, studies on the clinical efficacy and safety of this drug in the Chinese multiple myeloma (MM) population remain insufficient.

Objective: To investigate the clinical efficacy and safety of carfilzomib in the treatment of MM.

Methods: Fifty-three MM patients who received at least two cycles of carfilzomib treatment at Sichuan Provincial People' s Hospital between March 2022 and September 2023 were enrolled as study subjects. Baseline data were collected for all patients, who were treated with carfilzomib-based regimens. The time of first carfilzomib administration was defined as the starting point of follow-up, with death, disease relapse, or end of follow-up as the endpoint. Patients were followed up every two months through outpatient visits, inpatient re-examinations, or telephone calls. The numbers of patients achieving stringent complete response (sCR), complete response (CR), very good partial response (VGPR), and partial response (PR), as well as those experiencing adverse reactions were recorded. Overall response rate (ORR), ≥VGPR rate, best ORR, and best ≥VGPR rate were calculated to evaluate clinical efficacy. Subgroup efficacy analyses were performed based on treatment line, extramedullary disease, Durie-Salmon (DS) stage, International Staging System (ISS), renal function, and cardiovascular disease. Kaplan-Meier method was used to plot progression-free survival (PFS) and overall survival (OS) curves for survival analysis, with Log-rank test employed for curve comparison.

Results: After two treatment cycles, 17 patients achieved PR (32.1%), 11 achieved VGPR (20.8%), 4 achieved CR (7.5%), and 8 achieved sCR (15.1%), with an ORR of 75.5% (40/53). Overall efficacy assessment showed a best ORR of 84.9% (45/53) and a best ≥VGPR rate of 71.7% (38/53). No statistically significant difference was observed in overall clinical efficacy among

the first-line treatment group, first relapse treatment group, and third-line or beyond treatment group (P>0.05). The PFS curves among the three groups showed a statistically significant difference (P<0.05), while the OS curves showed no statistically significant difference (P>0.05). No statistically significant differences were found in clinical efficacy, PFS, or OS curves between mSMART standard-risk and high-risk groups, DS stage I–III groups, ISS stage I–III groups, extramedullary disease and non-extramedullary disease groups, cardiovascular disease and non-cardiovascular disease groups, or normal and abnormal renal function groups (P>0.05). Among the 53 patients, 8 (15.1%) experienced infections, 7 (1.2%) had adverse reactions such as elevated blood pressure, arrhythmia, or worsening heart failure, 3 (5.7%) developed gastrointestinal adverse reactions including nausea and vomiting, 1 (1.9%) had hepatic impairment, and 1 (1.9%) had renal impairment. The overall incidence of adverse reactions was 37.7% (20/53).

Conclusion: Carfilzomib-based chemotherapy regimens demonstrate favorable efficacy and safety, and can be considered as a preferred treatment option for patients with multiple myeloma.

Full Text

Introduction

Multiple myeloma (MM) is a common hematologic malignancy, accounting for approximately 10% of all blood cancers, with its incidence rising annually and showing a trend toward younger onset in China. The median overall survival (OS) for Chinese patients is 5 years, significantly lower than the 8–10 years reported internationally [1]. The clinical course of MM is characterized by repeated cycles of relapse and remission, with a 5-year relapse rate approaching 70%. Successive lines of therapy yield progressively lower response rates and shorter durations of remission [2-3]. Proteasome inhibitors represent the most commonly used class of drugs for MM treatment, utilized in 86% of first-line regimens [4]. Bortezomib is recommended as the preferred agent by both the NCCN guidelines [4] and the Chinese Multiple Myeloma Diagnosis and Treatment Guidelines (2022 revision) [5]. However, studies have demonstrated that retreatment with bortezomib produces minimal response, whereas the second-generation proteasome inhibitor carfilzomib has shown significant efficacy against relapsed and refractory multiple myeloma (RRMM) in multicenter clinical trials [6]. Since its approval in China in 2022, carfilzomib has been widely used in RRMM patients, yet real-world data on its effectiveness and safety in the Chinese MM population remain limited. This study investigates the clinical efficacy and safety of carfilzomib-based regimens by analyzing treatment data from MM patients to provide evidence for clinical decision-making.

Methods

Study Design and Participants

This single-center retrospective study enrolled 53 MM patients who received at least two cycles of carfilzomib treatment at Sichuan Provincial People's Hospital between March 2022 and September 2023.

Inclusion and Exclusion Criteria: Inclusion criteria comprised: (1) diagnosis of MM according to the Chinese Multiple Myeloma Diagnosis and Treatment Guidelines (2022 revision) [5] and receipt of at least two cycles of carfilzomib-based therapy; (2) age between 18 and 90 years; and (3) Eastern Cooperative Oncology Group (ECOG) performance status of 0–3 (including asymptomatic patients, those with mild symptoms, those without functional limitations but unable to work, and those with some degree of functional limitation). Exclusion criteria included: (1) pregnancy, planned pregnancy, or lactation; (2) concurrent malignancies; and (3) estimated survival time <1 year. The study was approved by the Ethics Committee of Sichuan Provincial People' s Hospital [Ethics Review (Research) No. 149 of 2024], and all patients provided informed consent.

Diagnostic and Staging Criteria: MM diagnosis followed the Chinese Multiple Myeloma Diagnosis and Treatment Guidelines (2022 revision) [5]. Disease staging was performed using the Durie-Salmon (DS) staging system [7], International Staging System (ISS) [8], and Mayo Stratification for Myeloma and Risk-Adapted Therapy (mSMART) 3.0 risk stratification system. The DS system includes stages I–III: Stage I requires (1) hemoglobin >100 g/L, (2) serum calcium $ 2.65mmol/L(11.5mg/dL), (3)normalbonestructureorsolitaryboneplasmacytomaonskeletalX-ray, and(4)lowserumorurinemyeloma proteinproduction; StageIIincludespatientsnotmeetingStageIorIIIcr 85g/L, (2)serumcalcium > 2.65mmol/L, (3)morethanthreelyticbonelesions, and(4)highserumorurinemyelon StageI($2-microglobulin <3.5 mg/L and albumin $ 35g/L), StageII(neitherStageInorIII), andStageIII($2- microglobulin $ 5.5mg/L).ThemSMARTsystemcategorizespatientsashigh − risk(presenceofanyhigh−riskcytogeneticabnormality : t(4; 16), t(14; 16), t(14; 20), del(17p), p53mutation, 1qa unrelated chromosomal abnormalities]) or standard-risk (all others). Renal insufficiency was defined as creatinine clearance <40 mL/min or serum creatinine >117 mol/L. Cardiovascular disease included hypertension, diabetes, coronary artery disease, or heart failure. Extramedullary disease (EMD) comprised soft tissue plasmacytomas from hematogenous dissemination (EMD-S) and paraosseous plasmacytomas extending from bone cortex destruction (EMD-B), excluding solitary plasmacytoma and primary plasma cell leukemia (PCL).

Treatment Regimens

All patients received carfilzomib-based therapy administered as intravenous infusions on two consecutive days weekly for three weeks, followed by a 12-day rest period, constituting a 28-day cycle. In cycle 1, carfilzomib 20 mg/m^2 was given on days 1–2; if tolerated, the dose was escalated to 27 mg/m^2 on day 8 of cycle 1, combined with dexamethasone 20 mg twice weekly. Combination

regimens are detailed in Table 1 .

Follow-up and Assessment

Patients were followed up through outpatient visits, hospital readmissions, or telephone contact every two months. The follow-up period began at the first carfilzomib administration and ended at death, disease relapse, or study conclusion (January 20, 2024). The median follow-up duration was 8.0 months (range 7.6–9.8 months). Hematologic response was evaluated according to the Chinese Multiple Myeloma Diagnosis and Treatment Guidelines (2022 revision) [5], recording stringent complete response (sCR), complete response (CR), very good partial response (VGPR), and partial response (PR). Progression-free survival (PFS) and overall survival (OS) were also documented. The overall response rate (ORR) was calculated as the sum of sCR, CR, VGPR, and PR rates after two cycles; the ≥VGPR rate was the sum of sCR, CR, and VGPR rates. Best ORR and best ≥VGPR rate represented the optimal responses achieved by the follow-up cutoff. PFS was defined as the interval from carfilzomib initiation to disease progression or last follow-up; OS was defined as the interval from initiation to death or last follow-up.

Safety Assessment: Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0) [9], documenting respiratory, gastrointestinal, circulatory, and urinary system toxicities.

Statistical Analysis

Data were analyzed using GraphPad Prism 8.0. Normally distributed continuous variables are presented as mean ± standard deviation and compared using ANOVA; non-normally distributed data are presented as median (P25, P75) and compared using rank-sum tests. Categorical data are expressed as proportions and compared using chi-square tests. Kaplan-Meier curves were generated for PFS and OS, with comparisons performed using log-rank tests. A P-value <0.05 was considered statistically significant.

Results

Baseline Characteristics

Among the 53 patients, 23 (43.4%) were male and 30 (56.6%) female, with a median age of 66 years (range 20–79). Carfilzomib was used as first-line therapy in 14 patients (26.4%), at first relapse in 20 (37.7%), and as third-line or later therapy in 14 (26.4%); five patients (9.4%) switched to carfilzomib due to adverse reactions to other agents. As of December 2023, 50 patients (94.3%) remained alive and 3 (5.7%) had died. No significant differences in age or sex were observed across subgroups stratified by treatment line, extramedullary

disease, DS stage, ISS stage, mSMART risk, or comorbidities (P>0.05) (Table 2 , Table 3).

Overall Clinical Efficacy

After two treatment cycles, 17 patients (32.1%) achieved PR, 11 (20.8%) VGPR, 4 (7.5%) CR, and 8 (15.1%) sCR, yielding an ORR of 75.5% (40/53). The best ORR was 84.9% (45/53) and the best ≥VGPR rate was 71.7% (38/53). The median PFS was 12.0 months (95% CI: 10.0–13.9) and median OS was 11.3 months (95% CI: 11.0–17.6).

Subgroup Analyses

Treatment Lines: No significant differences in overall efficacy were observed among first-line, first-relapse, and third-line or later groups (≥VGPR rate: ^{2}=0.341, P=0.483; ORR: ^{2}=1.088, P=0.580) (Table 3). However, PFS curves differed significantly among the three groups (^{2}=5.979, P=0.015), while OS curves did not (^{2}=0.455, P=0.293) (Figure 1 [Figure 1: see original paper]).

Extramedullary Disease: Efficacy did not differ significantly between patients with and without EMD (≥VGPR rate: ^{2}=0.050, P=0.823; ORR: ^{2}=0.640, P=0.424) (Table 4), nor did PFS or OS curves (PFS: ^{2}=0.039, P=0.843; OS: ^{2}=0.002, P=0.964) (Figure 2 [Figure 2: see original paper]).

mSMART Risk: Among 53 patients, 12 were mSMART standard-risk and 41 high-risk, including 27 (65.9%) with 1q amplification, 3 (7.3%) with p53 mutation, 3 (7.3%) with complex karyotype, 1 (2.4%) with del(17p), and 7 (17.1%) with double-hit disease. No significant differences in efficacy (≥VGPR rate: ^{2}=0.863, P=0.353; ORR: ^{2}=0.052, P=0.820) (Table 5), PFS (^{2}=1.967, P=0.161), or OS (^{2}=1.16, P=0.281) were observed between risk groups (Figure 3 [Figure 3: see original paper]).

DS Staging: No significant differences in efficacy were found across DS stages I-III (≥VGPR rate: ^{2}=1.187, P=0.552; ORR: ^{2}=0.405, P=0.817) (Table 6), nor in PFS (^{2}=1.585, P=0.45) or OS (^{2}=0.807, P=0.668) curves (Figure 4 [Figure 4: see original paper]).

ISS Staging: Efficacy did not differ significantly across ISS stages I-III (≥VGPR rate: ^{2}=0.460, P=0.793; ORR: ^{2}=2.366, P=0.306) (Table 7), with no differences in PFS (^{2}=1.441, P=0.486) or OS (^{2}=3.322, P=0.190) (Figure 5 [Figure 5: see original paper]).

Cardiovascular Disease: No significant efficacy differences were observed between patients with and without cardiovascular disease (≥VGPR rate: ^{2}=0.225, P=0.635; ORR: ^{2}=0.078, P=0.780) (Table 8), with comparable PFS (^{2}=0.402, P=0.526) and OS (^{2}=3.322, P=0.190) (Figure 6 [Figure 6: see original paper]).

Renal Function: Efficacy was similar between patients with normal and abnormal renal function (≥VGPR rate: ^{2}=0.098, P=0.754; ORR: ^{2}=2.705, P=0.100)

(Table 9), with no differences in PFS (^{2}=0.153, P=0.696) or OS (^{2}=1.150, P=0.283) (Figure 7 [Figure 7: see original paper]).

Safety Profile

The overall adverse event rate was 37.7% (20/53), with no treatment-related deaths, peripheral neuropathy, infusion reactions, or tumor lysis syndrome. Infections occurred in 8 patients (15.1%), including 6 (11.3%) with pulmonary infections and 2 (3.8%) with gastrointestinal infections. Cardiovascular events (hypertension, arrhythmia, worsening heart failure) occurred in 7 patients (13.2%). Gastrointestinal adverse reactions (nausea, vomiting) were observed in 3 patients (5.7%). Hepatic and renal dysfunction each occurred in 1 patient (1.9%).

Discussion

Multiple myeloma is a prevalent hematologic malignancy with increasing global incidence and incompletely understood etiology. While therapeutic advances over the past decade have substantially prolonged OS and PFS, MM remains incurable [10]. Proteasome inhibitors (PIs) constitute the cornerstone of MM therapy worldwide, and carfilzomib, a second-generation PI, exhibits high proteasome selectivity, conferring enhanced antitumor activity and a more favorable toxicity profile [11]. Since its FDA approval for RRMM in 2012, over a decade of real-world data have demonstrated its significant efficacy. However, real-world evidence from China remains limited. This study addresses this gap by analyzing clinical outcomes of carfilzomib-based regimens in Chinese MM patients.

Our findings show a best ORR of 84.9% and best ≥VGPR rate of 71.7%, which are modestly lower than international real-world data. An Italian multicenter retrospective study of 600 MM patients treated with KRd reported an ORR of 79.9% [12], while a US single-center study of 389 newly diagnosed MM patients achieved an ORR of 93.1% with KRd [13]. This discrepancy may reflect higher proportions of newly diagnosed patients in Western cohorts. Compared with clinical trials such as ASPIRE [14] (KRd: ORR 87.1%, ≥VGPR rate 70%), ENDEAVOR [15] (overall ORR 77%), and IKEMA [16] (Isa-Kd: ORR 88%, ≥VGPR rate 80%), our response rates are slightly lower. Real-world patients often have poorer performance status, more comorbidities, and treatment limitations due to tolerance and financial constraints, resulting in suboptimal adherence and reduced efficacy.

The median PFS of 12.0 months in our cohort is shorter than reported in ASPIRE [14] (KRd: 20.6 months), CANDOR [17] (Kd: 15.8 months), IKEMA [16] (Kd: 19.1 months), and ENDEAVOR [15] (Kd: 18.7 months). Several factors may explain this difference: (1) shorter median follow-up duration (8.0 months vs. longer follow-up in trials); (2) higher proportions of high-risk patients (56.6% mSMART high-risk) and EMD (32.1%), both associated with aggressive disease, poor drug response, and inferior survival; and (3) inclusion of heavily pretreated

patients with advanced disease burden.

Notably, carfilzomib demonstrated consistent efficacy across treatment lines, with no significant differences in ORR among first-line, first-relapse, and third-line or later groups. However, PFS curves differed significantly, suggesting that earlier carfilzomib use more effectively delays disease progression, consistent with findings from the FORTE trial [18] showing 4-year PFS of 71% with KRd in newly diagnosed MM. While OS curves showed no significant differences, likely due to short follow-up, the PFS benefit supports early carfilzomib integration.

Extramedullary disease, present in 32.1% of our cohort, represents a high-risk feature associated with adverse cytogenetics and poor prognosis [19]. Carfilzomib-based therapy achieved an ORR of 76.4% in EMD patients, with responses observed across skin, muscle, lymph node, and central nervous system involvement. Importantly, no significant differences in efficacy, PFS, or OS were observed between patients with and without EMD, indicating that carfilzomib can overcome this poor prognostic factor.

Similarly, mSMART high-risk and standard-risk patients showed comparable efficacy, PFS, and OS, suggesting carfilzomib mitigates the negative impact of high-risk cytogenetics. Subgroup analyses further demonstrated that advanced DS stage, ISS stage, renal insufficiency, and cardiovascular disease did not compromise efficacy or survival outcomes, underscoring carfilzomib' s broad applicability.

The safety profile was favorable, with an adverse event rate of 37.7% and no treatment-related mortality. Notably, no peripheral neuropathy, infusion reactions, or tumor lysis syndrome were observed. The most common toxicities were infections (15.1%) and cardiovascular events (13.2%), manageable with appropriate monitoring and supportive care.

This study has limitations, including the small sample size, heterogeneous treatment lines, and relatively short follow-up duration, which may affect prognostic analyses. Longer-term follow-up is warranted to determine optimal treatment sequencing and long-term outcomes.

In conclusion, real-world data demonstrate that carfilzomib-based regimens are effective and safe for Chinese MM patients, offering benefits in both newly diagnosed and relapsed/refractory settings. Carfilzomib shows activity against high-risk features including EMD and adverse cytogenetics, improving outcomes across diverse patient subgroups. With manageable toxicity in both younger and older patients, carfilzomib represents a preferred treatment option for MM.

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