Systematic Review and Meta-Analysis

Medicine

OPEN

Efficacy and toxicity of carfilzomib- or bortezomib-based regimens for treatment of transplant-ineligible patients with newly diagnosed multiple myeloma

A meta-analysis

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Abstract

Background: Multiple myeloma is a clonal disorder of malignant plasma cells that comprises approximately 10% of hematologic malignancies. The aim of this study was to investigate the efficacy and toxicity of carfilzomib- or bortezomib-based regimens for treatment of transplant-ineligible patients with newly diagnosed multiple myeloma by performing a meta-analysis of randomized controlled trials (RCTs).

Methods: Data mining was conducted in March 2022 across PubMed, EMBASE and ClinicalTrials.gov. All published RCTs which assessed efficacy and toxicity of carfilzomib-based regimens treatment for transplant-ineligible patients with newly diagnosed multiple myeloma when compared with a bortezomib-based regimens were included.

Results: Our meta-analysis showed that the overall response rate (ORR) (Odds ratio = 1.33, 95% CI 1.05–1.69, $P = .02$) was significantly higher in the carfilzomib-based regimens group than in the bortezomib-based regimens group. However, the difference in ORR did not translate into improvements in progression-free survival (PFS), overall survival (OS) and complete response rate (CRR). Adverse events of grade 3 or worse that occurred with a higher incidence in the carfilzomib-based regimens group compared with the bortezomib-based regimens group were dyspnea, hypertension, acute kidney injury, and heart failure.

Conclusions: The carfilzomib-based regimens did not improve PFS, OS and CRR compared with the bortezomib-based regimens in transplant-ineligible patients with newly diagnosed multiple myeloma, and they showed higher toxicity.

Abbreviations: CIs = confidence intervals, CRR = complete response rate, HR = hazard ratio, ORR = overall response rate, OS = overall survival, PFS = progression-free survival, PN = peripheral neuropathy.

Keywords: bortezomib, carfilzomib, meta-analysis, multiple myeloma

1. Introduction

Multiple myeloma is a clonal disorder of malignant plasma cells that comprises approximately 10% of hematologic malignancies. Multiple myeloma results from clonal proliferation of neoplastic plasma cells in the bone marrow and production of monoclonal immunoglobulins, leading to end organ damage. The age-standardized incidence rate of the disease was 2.1 per 100 000 people worldwide in 2016, and about 160 000 patients had newly diagnosed multiple myeloma in 2018.[1,2] In the United States, the age-standardized incidence rate (7.1 per 100 000 people) was higher than the global rate in 2016,[3] and incidence rates have gradually increased, which is consistent with the global trend.[4] Additionally, multiple myeloma is slightly more common in men than in women, and it is twice as common in Black than in White individuals.[5] The median age of patients at the time of diagnosis is about 65 years.[6] Although important modifications and improvements have taken place regarding treatment in recent years,[7,8] and even if median survival is not so brief, most patients relapse.[9]

High dose chemotherapy plus autologous stem cell transplantation is an effective and widely used treatment option for multiple myeloma in younger patients. High dose chemotherapy plus autologous stem cell transplantation was considered responsible for improving the overall survival (OS) prior to introduction of novel agents.[10] Although high dose chemotherapy plus autologous stem cell transplantation has been recommended for multiple myeloma in younger patients, some

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

The authors have no funding and conflicts of interest to disclose.

Supplemental Digital Content is available for this article.

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How to cite this article: Xie C, Wei M, Yang F, Liu Q, Wu F, Huang J. Efficacy and toxicity of carfilzomib- or bortezomib-based regimens for treatment of transplant-ineligible patients with newly diagnosed multiple myeloma: A meta-analysis. Medicine 2022;101:39(e30715).

Received: 18 July 2022 / Received in final form: 23 August 2022 / Accepted: 24 August 2022

http://dx.doi.org/10.1097/MD.0000000000030715

patients might be not suitable for transplantation because of co-morbidities, frailty, or limited financial resources.[1] High dose chemotherapy plus autologous stem cell transplantation is an option for fit patients with relapsed disease that is refractory to standard options, and in rare situations such as clinical trials for young and fit patients with newly diagnosed multiple myeloma with high-risk disease as a consolidation approach. This option, however, is not routinely recommended.[11,12] Therefore, patients manifest recurrent and refractory multiple myeloma, the treatment of which presents a substantial challenge. New anti-myeloma drugs have an improved efficacy and reduced side effects, and they help in improving the prognosis of patients with multiple myeloma.[13] These novel agents include proteasome inhibitors (Bortezomib, Carfilzomib and Ixazomib) and immunomodulatory drugs (IMiDs) (Thalidomide, Lenalidomide, Pomalidomide), are effective in treating refractory and recurrent multiple myeloma.[13]

Bortezomib is now an important component of anti-myeloma therapy. The results of the VISTA study indicated that bortezomib plus melphalan and prednisone produced markedly higher response rates (complete response rate (CRR): 30% vs 4%, $P < .001$; partial response rate (PRR): 71% vs 35%, $P < .001$), longer time to progression (24.0 months vs 16.6 months; Hazard ratio (HR): 0.48, $P < .001$), and better 3-year OS (68.5% vs 54%, $P = .0008$) compared with melphalan and prednisone alone.[14,15] An updated analysis of the data with a median follow-up of five years demonstrated 13.3 months higher median OS in patients treated with bortezomib plus melphalan and prednisone compared with those treated with melphalan and prednisone alone (56.4 months vs 43.1 months).[16] Based on these data, bortezomib plus melphalan and prednisone is recognized as a standard of care regimen for use in multiple myeloma patients. However, 47% of bortezomib-treated patients reported peripheral neuropathy (PN) and 22% of patients required bortezomib dose reductions because of this adverse event.[17] Additionally, in the ENDEAVOR study, combined bortezomib and dexamethasone treatment did not result in better progression-free survival (PFS) and OS compared with carfilzomib- dexamethasone in patients with relapsed or refractory multiple myeloma.[18]

Carfilzomib is a second-generation proteasome-inhibitor initially approved in 2013 for the treatment of relapsed refractory multiple myeloma in patients previously treated with lenalidomide and bortezomib, and it might be more potent than bortezomib.[19] The first prospective phase 1/2 study of the combination carfilzomib-melphalan-prednisone treatment in transplant-ineligible patients with newly diagnosed multiple myeloma showed acceptable tolerability with a low peripheral neuropathy rate.[20] The maximum tolerated dose of carfilzomib was 36 mg/m^2, at which a promising overall response rate (ORR) of 90% and a satisfactory median PFS of 21 months were observed.[20] In another randomized trial for relapsed multiple myeloma, carfilzomib plus dexamethasone was associated with an improvement in PFS and OS compared with bortezomib carfilzomib plus dexamethasone.[18,21] However, the dose of carfilzomib used in that trial (56 mg/m^2) was almost twice as high as the standard dose, thereby carrying a much higher cost compared with bortezomib. Moreover, a recent randomized, phase 3 trial (CLARION study) comparing carfilzomib-melphalan-prednisone with bortezomib-melphalan-prednisone did not show a benefit for carfilzomib when used as the primary therapy in the patients with multiple myeloma who were ineligible for autologous stem cell transplantation.[22] A systematic review and meta-analysis of relevant similar trials is needed to clarify the efficacy and safety of carfilzomib. Moreover, analysis of combined data from randomized controlled trials (RCTs) will also enable greater precision in making an unbiased estimate of the treatment effects.

Therefore, we assessed the efficacy and toxicity profile of carfilzomib-based regimens in comparison to bortezomib-based regimens in transplant-ineligible patients with newly diagnosed multiple myeloma.

2. Methods

All steps of this review were performed in strict accordance with the Cochrane Handbook for Systematic Reviews of Interventions.[23] The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement guidelines were followed during the meta-analysis and preparation of this review.[24]

2.1. Search strategy

As of March 2022, we searched PubMed, EMBASE, and ClinicalTrials.gov (www.clinicaltrials.gov). Search terms included ("Bortezomib OR velcade") AND "Carfilzomib" AND "myelom*" AND"random*". Titles and abstracts were screened by two independent reviewers, and then the full-text of potentially relevant articles were retrieved for further evaluation. The decision to include a study was made by two independent reviewers after full-text review. The reference lists of the included articles were further hand-searched to identify additional relevant articles.

2.2. Eligibility criteria and study selection

We included all clinical trials meeting the following criteria: RCTs involving transplant-ineligible patients primarily diagnosed with multiple myeloma who were newly diagnosed, that is, did not receive any prior therapy; and RCTs comparing outcomes in efficacy and toxicity between carfilzomib-based regimens versus bortezomib-based regimens. We excluded the following: retrospective and observational studies; non-human studies; studies that did not report the key end-points (CRR, ORR, PFS, or OS). Eligibility screening was performed in two steps, each by two independent reviewers. First, title and abstract screening for relevance to the study objective was conducted, which was followed by full-text screening for eligibility for a meta-analysis. Conflicts were resolved by the opinion of a third reviewer.

2.3. Outcomes

2.3.1. Efficacy measures. OS was defined as the time from the date of randomization to the date of death (from any cause). PFS was defined as the time from the date of randomization to the date of progression or death (from any cause). ORR and CRR represented the proportion of patients with overall response or complete response, according to the International Myeloma Working Group uniform response criteria.

2.3.2. Toxicity measures. Averse events of grade 3 or higher, as defined by the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), were included in the analysis.

2.4. Data extraction

Two independent reviewers extracted the following data from the included studies: baseline characteristics of enrolled patients, general characteristics of the study design, and information on efficacy and safety outcomes. Data were summarized by one investigator and checked by the second reviewer. Any discrepant data were reexamined by a third reviewer to ensure data accuracy.

2.5. Assessment of the risk of bias

The risk of bias within each study was assessed by two independent reviewers using the Cochrane Risk of Bias assessment tool, as described in the Cochrane Handbook for Systematic Reviews of Interventions 5.1.0.[24] This tool classifies the studies as having low, unclear, or high risk of bias across six domains that include sequence generation, allocation concealment, blinding, missing data, selective reporting, and other biases.

2.6. Data analysis

The meta-analysis was conducted using RevMan 5.3 software (Cochrane Collaboration, London, UK). For time-to-event outcomes data (OS and PFS), we extracted the HR and 95% confidence intervals (CIs) from the included studies and calculated the overall HRs and 95% CIs for combined studies using methods recommended in the Cochrane Handbook for Systematic Reviews of Interventions. For dichotomous outcomes data (ORR and CRR), we analyzed the data as Odds ratios (ORs) with 95% CIs. Averse events were reported in each included trial according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE). The number of grade 3/4 adverse events was reported as a percentage (%) of the total number of patients on each arm in each included trial. Therefore, we assumed that each adverse event was counted once, so we analyzed these data as dichotomous data. The statistical heterogeneity among trials was measured by Q statistics and the I^2 test. Higher I^2 values indicated greater heterogeneity, with I^2 values of 25, 50, and 75% signifying mild, moderate, and high heterogeneity, respectively.[25–27] Publication bias could be assessed by visual inspection of a funnel plot, and the Egger test was used to evaluate publication biases. However, according to Egger and colleagues, assessing publication bias using the funnel plot-based methods is not reliable when fewer than 10 pooled studies are used in the direct comparison.[28] Only two studies were included in this meta-analysis, so the funnel plot should be not reported.

2.7. Ethics and dissemination

Ethics approval was not required for this meta-analysis because of the data used does not include personal data. Therefore, there were no concerns about privacy.

3. Results

3.1. Search results

We identified 718 references from the electronic literature search. After screening the titles and abstracts, 698 were excluded because they failed to meet the inclusion criteria. By reading the full text of the remaining 20 articles, 18 articles were excluded: one study included patients with relapsed or refractory multiple myeloma; another one constituted a conference abstract and did not provide treatment outcomes; and 16 studies were eliminated because they were review articles. Ultimately, only two studies (CLARION study and ENDURANCE trial) that fully satisfied the pre-established inclusion criteria of this meta-analysis were included (Figure S1, Supplemental Digital Content 1, http://links.lww.com/MD/H380).[22,29]

3.2. Study characteristics

The two included studies were CLARION (carfilzomib-melphalan-prednisone vs bortezomib-melphalan-prednisone) and ENDURANCE (carfilzomib-lenalidomide-dexamethasone vs or bortezomib-lenalidomide-dexamethasone), and they were published between 2019 and 2020.[22,29] The collective patient population from North America, Europe, Asia-Pacific, Mexico, Argentina, and Israel with 455 centers comprised 1023 individuals in the carfilzomib-based regimens group and 1019 individuals in the bortezomib-based regimens group. The mean age of participants ranged from 64 to 72 years. All studies were characterized by a preponderance of female subjects, with proportions ranging from 50% to 60%. All studies were performed in patients with newly diagnosed multiple myeloma.

3.3. Study quality

The risks of bias in each study are summarized in Table S1, Supplemental Digital Content 2, http://links.lww.com/MD/H381. Both studies claimed randomization, and two articles described the method of random sequence generation (random number table, computer generated). Two trials provided information that allowed us to assess whether an adequate concealment of the allocation procedure was used. All studies were open-label.

3.4. Efficacy

3.4.1. OS and PFS. In terms of OS, two studies were included in the analysis. In the comparison of carfilzomib-based regimens and bortezomib-based regimens, an analysis of 2042 patients produced no statistically significant differences in the OS (HR = 1.04, 95% CI 0.84–1.28, $P = .73$) for patients receiving carfilzomib-based regimens (Fig. 1A). Likewise, the data from the two studies included in the analysis did not show statistically significant differences in the PFS (HR = 0.96, 95% CI 0.83–1.11, $P = .59$) for patients receiving carfilzomib-based regimens compared with bortezomib-based regimens (Fig. 1B).

3.4.2. ORR and CRR. Based on the data from the two studies included in the analysis (2008 patients), there was significantly higher ORR (OR = 1.33, 95% CI 1.05–1.69, $P = .02$) for patients receiving carfilzomib-based regimens (Fig. 2A). However, for the CRR, the comparison of carfilzomib-based and bortezomib-based regimens produced no statistically significant difference (OR = 1.22, 95% CI 0.98–1.52, $P = .08$) (Fig. 2B).

3.4.3. Toxicity: adverse events. All included trials reported a frequency of grade 3 or worse adverse events. Most of grade 3 or worse adverse events occurring in at least 1% of patients treated by carfilzomib-based regimens versus bortezomib-based regimens are shown in Table 1. Adverse events of grade 3 or worse that occurred with a higher incidence in the carfilzomib-based regimens group compared with the bortezomib-based regimens group were dyspnea, hypertension, acute kidney injury, and heart failure. Adverse events of grade 3 or worse that occurred with a higher incidence in the bortezomib-based regimens group compared with the carfilzomib-based regimens group were neutropenia, thrombocytopenia, and PN.

4. Discussion

The aim of this systematic review and meta-analysis was to synthesize all available evidence on carfilzomib-based regimens versus bortezomib-based regimens for transplant-ineligible patients with newly diagnosed multiple myeloma. We identified two eligible RCTs that included 2042 participants. The overall risk of bias was moderate because these RCTs were open-label studies. CRR, OS and PFS were similar between the carfilzomib-based regimens and bortezomib-based regimens; however, more patients in the carfilzomib-based regimens group had an ORR. Grade 3–5 adverse events were reported more often in the carfilzomib-based regimens group than in the bortezomib-based regimens group. The carfilzomib-based regimens were associated with a higher prevalence of cardiac and renal treatment-related adverse events compared with the bortezomib-based regimens

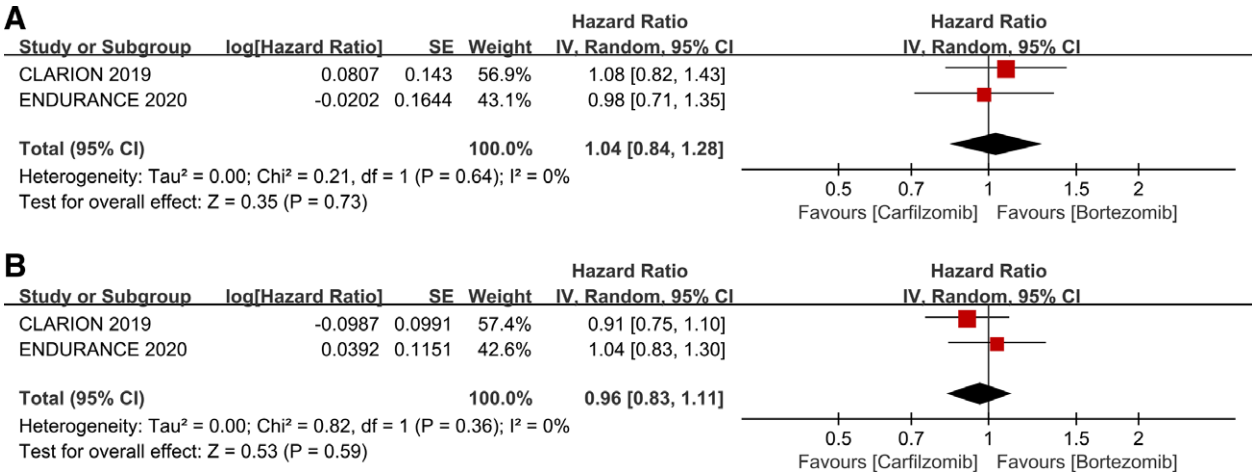

Figure 1. Hazard ratios (HRs) and 95% confidence intervals (CIs) of the individual studies and the pooled data for overall survival (A) and progression-free survival (B).

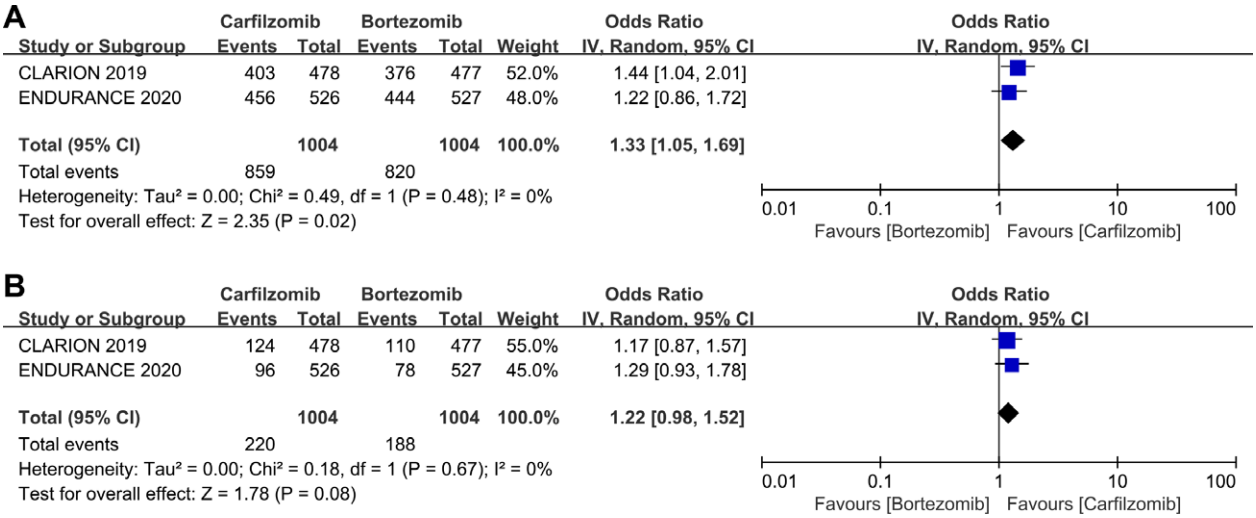

Figure 2. Odds ratios (ORs) and 95% confidence intervals (CIs) of the individual studies and the pooled data for overall response rate (A) and complete response rate (B).

Table 1

Treatment-emergent adverse events (Grade 3 or higher) in all patients.

Adverse events	Carfilzomib-based regimens	Bortezomib-based regimens	Odds ratio (95% CI)	*P* value
Anemia	80/474	64/470	1.29 [0.90, 1.84]	.16
Neutropenia	118/1000	152/997	0.71 [0.54, 0.94]	.01
Thrombocytopenia	80/1000	111/997	0.67 [0.49, 0.92]	.01
Acute kidney injury	34/1000	10/997	3.42 [1.67, 6.99]	.001
Diarrhea	22/1000	50/997	0.40 [0.12, 1.26]	.12
Dyspnea	54/1000	12/997	4.71 [2.50, 8.88]	.001
Fatigue	35/1000	51/997	0.59 [0.25, 1.40]	.23
Heart failure	46/1000	13/997	3.64 [1.95, 6.79]	.001
Hypertension	65/1000	25/997	2.68 [1.67, 4.30]	.001
Peripheral neuropathy	5/1000	81/997	0.06 [0.02, 0.17]	.001
Pneumonia	51/1000	37/997	1.40 [0.90, 2.18]	.14

CI = confidence interval.

group, but carfilzomib was associated with a lower prevalence of PN and hematological adverse events.

On the basis of previous single-arm phase 2 studies of the carfilzomib regimen in patients with multiple myeloma, we anticipated that the carfilzomib-based regimens would improve outcomes compared with the bortezomib-based regimens. The Intergroupe Francophone du Myelome conducted a phase 2 study evaluating carfilzomib plus lenalidomide and

dexamethasone in patients with newly diagnosed multiple myeloma.[30] The patients received four carfilzomib plus lenalidomide and dexamethasone induction cycles, autologous stem cell transplantation, four carfilzomib plus lenalidomide and dexamethasone consolidation cycles, and 1-year lenalidomide maintenance. Carfilzomib (20/36 mg/m^2) was given for 3 weeks of each 4-week cycle. Post-consolidation ORR was 97.5%, including 23.5% patients of very good PRR and 69% patients of CRR. The minimal residual disease negativity rate was 70% by flow cytometry. Median PFS was not reached; the 2-year PFS rate was 91% (31). In another phase 2 trial of 53 patients with newly diagnosed multiple myeloma,[31] 28 (78%) of 36 patients completing eight or more cycles of carfilzomib plus lenalidomide and dexamethasone had near complete responses or better, and 22 (61%) had stringent complete responses. Estimated PFS at 24 months was 92%.[31] Moreau et al conducted a phase 1/2 study with carfilzomib plus melphalan and prednisone in 50 patients.[20] Among 50 efficacy-evaluable patients treated at the maximal tolerated dose, the ORR was 90%. The projected 3-year overall survival rate was 80%.[20] The most common hematological adverse events were neutropenia (38%), anemia (35%), and thrombocytopenia (28%).[20] Hence, the ORR of 85% observed in the carfilzomib-based regimens group in our study was consistent with the previous phase 2 studies.[20,31] Although the ORR was significantly higher in the carfilzomib-based regimens group than in the bortezomib-based regimens group in our study, this difference in ORR did not translate into improvements in PFS or OS. A potential hypothesis for the simultaneous trend of ORR benefit and lack of PFS benefit in the carfilzomib-based regimens group stems from the fact that carfilzomib-based regimens were less well tolerated than bortezomib-based regimens, which might have led to delays in treatment and modifications of dosage, thereby compromising the overall efficacy. Additionally, the smaller previous single-arm phase 2 trials of the carfilzomib-based regimens probably included highly selected patients, and were conducted at academic centers with better expertise at managing toxicities related to carfilzomib.[29] The results of our study, which was a meta-analysis of two large RCTs conducted primarily in oncology practices based in the community, provide a better assessment of the real-world efficacy of carfilzomib regimens.

Tolerability is a key concern for patients with newly diagnosed multiple myeloma. In our study, adverse events of grade 3 or worse that occurred with a higher incidence in the carfilzomib-based than in the bortezomib-based regimens group were dyspnea, hypertension, acute kidney injury, and heart failure. Our results are consistent with those reported in previous studies.[18,32,33] Cardiac failure and acute renal failure are serious concerns for patients with multiple myeloma that lead to discontinuation of therapy in a number of patients. However, the pathophysiology of carfilzomib-mediated cardiotoxicity is not clearly understood, with studies suggesting several potential mechanisms.[34] Of note, neurotoxicity observed in patients treated by bortezomib-based regimens in our study was consistent with those reported by previous study,[35,36] with 8% of patients developing grade 3 or worse peripheral neuropathy.

Our study has limitations. First, the total number of clinical trials contributing to this meta-analysis is small, nevertheless, Cochrane Consumers and Communication Group indicated that two studies is a sufficient number to perform a meta-analysis.[37] Second, the included trials were not blinded, so it is possible that the knowledge of the treatment assignment might have influenced clinical decision-making, which could have affected the ordinal measurements we used. Finally, longer follow-up is needed to ascertain whether differences in OS would emerge between the treatment groups.

5. Conclusions

In conclusion, our study found that there were no statistically significant differences in PFS, OS, and CRR between the carfilzomib-based regimens and bortezomib-based regimens in transplant-ineligible patients with newly diagnosed multiple myeloma. Increased toxicity in the carfilzomib-based regimens may explain clinical outcomes. Thus, our results suggest that carfilzomib demonstrates comparable efficacy to bortezomib, but with a much more adverse events of dyspnea, hypertension, acute kidney injury, and heart failure in newly diagnosed multiple myeloma. Alternative carfilzomib-based regimens merit further evaluation in transplant-ineligible patients with newly diagnosed multiple myeloma.

Acknowledgment

We thank LetPub (www.letpub.com) for its linguistic assistance during the preparation of this manuscript.

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All authors provided final approval and agree to be account able for the work.
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