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ORIGINAL RESEARCH

Subcutaneous bortezomib might be standard of care for patients with multiple myeloma: a systematic review and meta-analysis

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Background: Administration of subcutaneous (SC) bortezomib in patients with multiple myeloma (MM) has increased in recent years. Yet, it is unclear whether there is sufficient evidence to support the use of SC bortezomib as a standard of care.

Methods: A systematic review of 4 randomized controlled trials and 8 retrospective trials comparing SC to intravenous (IV) bortezomib among 1,857 MM patients was performed. Embase, PubMed, Clinical Trials.gov, Cochrane Library and reference lists were searched for relevant studies from inception until August 2018. Outcomes of interest included 1-year overall survival (OS), 1-year progression-free survival (PFS), objective response rate (ORR) and adverse events (AEs). Random events meta-analyses were performed. We also performed sensitivity analysis to examine whether the results of the meta-analysis were robust.

Results: Compared to IV administration, SC bortezomib had a significantly lower incidence of some all-grade or grade 3–4 AE, such as peripheral sensory neuropathy, leukopenia and thrombocytopenia ($p<0.05$). There was no statistical difference in 1-year OS, 1-year PFS, ORR between SC and IV bortezomib ($p>0.05$).

Conclusion: The data presented so far consistently show that SC bortezomib has become a standard of care for patients with MM.

Keywords: subcutaneous bortezomib, intravenous bortezomib, multiple myeloma, efficacy, adverse events, systematic review

Introduction

Multiple myeloma (MM) is characterized by the neoplastic proliferation of plasma cells producing a monoclonal immunoglobulin. MM accounts for approximately 1–2% of all cancers and slightly more than 17% of hematologic malignancies in the United States.[1] Worldwide, there are approximately 154,000 cases and 101,000 deaths per year attributed to MM.[2] Proteasome inhibitor bortezomib-based treatment has been used in both newly diagnosed MM[3] and relapsed or refractory MM[4] and elicited a high response rate. Despite their widespread use, adverse events (AEs) (eg, peripheral neuropathy) are common and there are still questions concerning their optimal regimen.

Initially, bortezomib is administered through intravenous (IV) infusion from the time of diagnosis of MM until patients are eligible for autologous hematopoietic cell transplantation.[5] This administration route was compared to the subcutaneous (SC) bortezomib in studies performed on patients with MM. Given the concerns regarding the toxicity of bortezomib, there has been increasing interest from oncologists and patients in finding the optimal administration route.

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A previous meta-analysis showed that a number of studies have investigated the efficacy and safety of SC bortezomib administered through IV administration route, but some studies are only abstract, with the outcomes of efficacy being only in objective response rate (ORR). Also, one trial included[6] was different from the other trials (in one trial the SC bortezomib was administered once a week, but the others were twice a week); these might affect the final results.[7] As there is now more data available, a systematic review and meta-analysis were performed in order to assess whether or not the SC administration route of bortezomib should be considered as a standard of care in patients with MM.

Methods

Search strategy

To obtain the studies that compared SC and IV bortezomib, we conducted a comprehensive literature search on Embase, PubMed, the Clinicaltrials.gov (http://clinicaltrials.gov/) and the Cochrane Library for all reported clinical trials published up to August 2018. The search terms included "bortezomib", "Velcade", "SC", "subcutaneous injection", "IV", "intravenous infusion", "multiple myeloma". We also screened the reference lists of review articles. Additional studies were also retrieved by manual search in relevant journals. We exclusively included studies which were published in English and Chinese.

Inclusion criteria and exclusion criteria

Studies were selected according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[8] Clinical trials that met the following criteria were included as follows:

(1) Randomized phase Ⅱ, Ⅲ, and Ⅳ trials

(2) Patients with MM (newly diagnosed, relapsed, or refractory)

(3) Participants who received SC bortezomib compared to IV bortezomib

(4) Events and event rates and sample sizes available for drug efficacy and safety

Exclusion criteria were as follows: (1) animal research; (2) reviews; (3) only have abstracts; (4) overlapping data; (5) studies without risk ratio (RR), OR or HR with 95% CIs.

Data extraction and quality assessment

Two reviewers independently conducted the literature screening, data extraction and quality assessment of the trials. A third reviewer intervened when reviewers disagreed until a consensus was reached. We extracted the following information from each article: first author's name, year of publication, study type, disease type, the number of patients, trial phase, treatment and control arms, the number of patients with 1-year overall survival (OS), 1-year progression-free survival (PFS), ORR and AEs. If the studies did not provide the 1-year OS or PFS data, we estimated those values from the Kaplan–Meier curve by using Engauge Digitizer software. The quality of the methodology in prospective trials was assessed by the Jadad criteria.[9] The quality of each trial was graded, with high-quality trials (score ≥3) and low-quality trials (score ≤2). The Newcastle–Ottawa Scale criteria (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp) were used to assess the quality of the methodology in retrospective studies (range 0–9 stars). High-quality classified as those with a score of ≥7 stars.

Statistical analysis

Data of patients with 1-year OS, 1-year PFS, ORR and AEs were extracted from all of the included trials. RR and 95%CI were calculated to assess the association strength of these two regimens with outcomes. The Q statistic and I^2 statistic were used to assess the heterogeneity. I^2>50% indicated statistically significant heterogeneity. The random-effect model was used in these meta-analyses for conservative statistics. A funnel plot was used to assess the publication bias. We also performed sensitivity analysis to examine whether the results of the meta-analysis were robust. Begg adjusted rank correlation test[10] and Egger regression test.[11] A statistical test with a p<0.05 was considered significant. STATA statistical version 12.0 was used to perform all the statistical analyses (Stata Corporation, College Station, Texas, USA). All p-values were two-sided.

Results

Characteristics of studies included in this study

Our search yielded a total of 1,187 potentially relevant clinical trials on SC or IV administration of bortezomib in patients with MM. After reviewing and screening, 12 primary studies, which included 1,857 subjects, met our inclusion criteria[12-22] and were pooled for the meta-analyses (Figure 1). The baseline characteristics of each trial are shown in Table 1; 4 RCTs and 8 retrospective trials were included. All trials included were

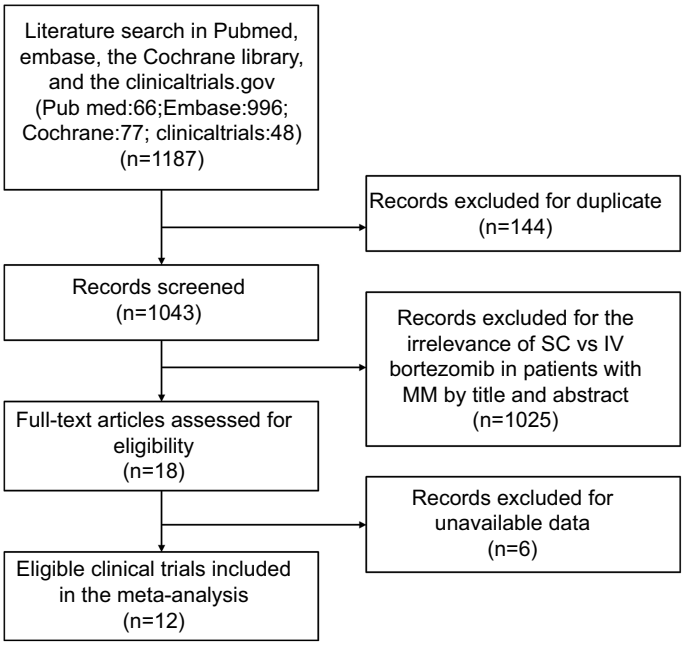

Figure 1 Flow chart for eligible studies.
Abbreviations: SC, subcutaneous injection; IV, intravenous infusion; MM, multiple myeloma.

open label. The number of enrolled patients ranged from 24 to 584. The quality of the included RCTs (Jadad scores) ranged from 2 to 3 and retrospective trials (NOS scores) ranged from 7 to 8 stars. According to the eligibility criteria of the majority of the trials, patients with impaired hepatic, renal or bone marrow function were excluded and most of the patients had Eastern Cooperative Oncology Group performance-status scores of 0 or 1. This systematic review followed the guidelines of the PRISMA statement.

Findings: 1-year OS, 1-year PFS and ORR

A total of 771 subjects who were treated with SC or IV bortezomib in 5 trials were used for the analysis of 1-year OS. Data from the 1-year OS between SC bortezomib and IV bortezomib arms produced a summary RR of 1.02 (95%CI: 0.95, 1.09, I^2=0%) (Figure 2A). The results showed no statistical difference in 1-year OS between SC and IV bortezomib (p=0.617).

A total of 670 subjects who were treated with SC or IV bortezomib in 4 trials were used for the analysis of 1-year PFS. Data from 1-year PFS between SC bortezomib and IV bortezomib arms produced a summary RR of 1.00 (95%CI: 0.88, 1.13, I^2=0%) (Figure 2B). The results showed no statistical difference in 1-year PFS between SC and IV bortezomib (p=0.967).

A total of 1,635 subjects treated with SC or IV bortezomib in 11 trials were used for the analysis of ORR. Data for ORR between SC bortezomib and IV bortezomib arms produced a summary RR of 0.99 (95%CI: 0.95, 1.03, I^2=0%) (Figure 2C). The results showed no statistical difference in ORR between SC and IV bortezomib (p=0.676).

Findings: adverse events

A number of different AEs and toxicities were reported. In the meta-analysis, patients treated with SC or IV bortezomib from 10 studies were included for analysis of all-grade or grade 3–4 AEs. As shown in Table 2, the overall RR of all-grade peripheral sensory neuropathy, leukopenia, asthenia, fatigue, infection, hepatobiliary disorders and thrombocytopenia between SC and IV bortezomib arms were 0.72 (95% CI: 0.62, 0.84, I^2=13.8%), 0.77 (95% CI: 0.60, 0.99, I^2=68.3%), 0.85 (95% CI: 0.72, 1.00, I^2=0%), 0.65 (95% CI: 0.51, 0.83, I^2=27.1%), 0.64 (95% CI: 0.46, 0.89, I^2=0%), 0.53 (95% CI: 0.35, 0.81, I^2=0%), and 0.68 (95% CI: 0.50, 0.94, I^2=70.3%). The overall RR of grade 3–4 peripheral sensory neuropathy, diarrhea, leukopenia, constipation, fatigue, neuralgia and thrombocytopenia between SC and IV bortezomib arms were 0.36 (95% CI: 0.25, 0.52, I^2=0%), 0.37 (95% CI: 0.20, 0.72, I^2=0%), 0.41 (95% CI: 0.28, 0.62, I^2=10.1%), 0.27 (95% CI: 0.10, 0.73, I^2=0%), 0.45 (95% CI: 0.23, 0.85, I^2=0%), 0.36 (95% CI: 0.13, 0.97,

Table 1 Characteristics of all studies

Study	Area	Tumor type	Trial type	Number SC/IV	Age (year) SC/IV	Interventions (days 1, 4, 8, 11)		Treatment regimens	Outcomes	Jadad score	NOS score
						SC	IV				
Moreau 2011	Mainly Europe	RRMM	RCTs	148/74	64.5	1.3 mg/m^2	1.3 mg/m^2	Bortezomib	ORR, 1-year PFS, 1-year OS, AE	3	
Moreau 2008	Europe	RRMM	RCTs	12/12	61	1.3 mg/m^2	1.3 mg/m^2	Bortezomib	ORR, AE	2	
Arnulf 2012	Europe	RRMM	RCTs	148/74	64.5	1.3 mg/m^2	1.3 mg/m^2	Bortezomib	ORR, 1-year PFS, 1-year OS, AE	3	
Merz 2015	Europe	NDMM	RCTs	280/304	59	1.3 mg/m^2	1.3 mg/m^2	PAd, VCD	ORR, AE	3	
Xu 2018	Asia	NDMM	Retrospective trials	167/140	56	1.3 mg/m^2	1.3 mg/m^2	PAd, BCd	ORR, 1-year PFS, 1-year OS, AE		8
Koh 2014	Asia	MM	Retrospective trials	28/73	64.5/65	1.3 mg/m^2	1.3 mg/m^2	VD, VMP, PAd, VTD	ORR, 1-year OS		7
Lamm 2013	Europe	NDMM	Retrospective trials	14/16	64/51	1.3 mg/m^2	1.3 mg/m^2	VTD, VMP, PAd	ORR, AE		7
Wu 2015	Asia	NDMM	Retrospective trials	30/30	57/54	1.3 mg/m^2	1.3 mg/m^2	VTD	ORR, 1-year PFS, 1-year OS, AE		8
Sidana 2017	North America	NDMM	Retrospective trials	17/147	66/60	1.3 mg/m^2	1.3 mg/m^2	Bortezomib-based treatments	ORR, AE		7
Liu 2013	Asia	MM	Retrospective trials	18/18	58/52	1.3 mg/m^2	1.3 mg/m^2	PAd	ORR, AE		7
Qin 2014	Asia	MM	Retrospective trials	12/14	61.5/64	1.0–1.3 mg/m^2	1.0–1.3 mg/m^2	VTD	ORR, AE		7
Liu 2016	Asia	MM	Retrospective trials	37/44	63/64	1.3 mg/m^2	1.3 mg/m^2	VTD	ORR, 1-year PFS, 1-year OS, AE		8

Abbreviations: MM, multiple myeloma; NDMM, newly diagnosed MM; RRMM, relapsed and/or refractory MM; PAd, bortezomib, doxorubicin, dexamethasone; VCD, cyclophosphamide, bortezomib, dexamethasone; VD, bortezomib, dexamethasone; VTD, bortezomib, dexamethasone, thalidomide; BCd, bortezomib, cyclophosphamide, dexamethasone; VMP, bortezomib, melphalan, prednisolone; ORR, objective response rate; PFS, progression-free survival; OS, overall survival; AE, adverse event; SC, subcutaneous; IV, intravenous; NOS, Newcastle-Ottawa Scale.

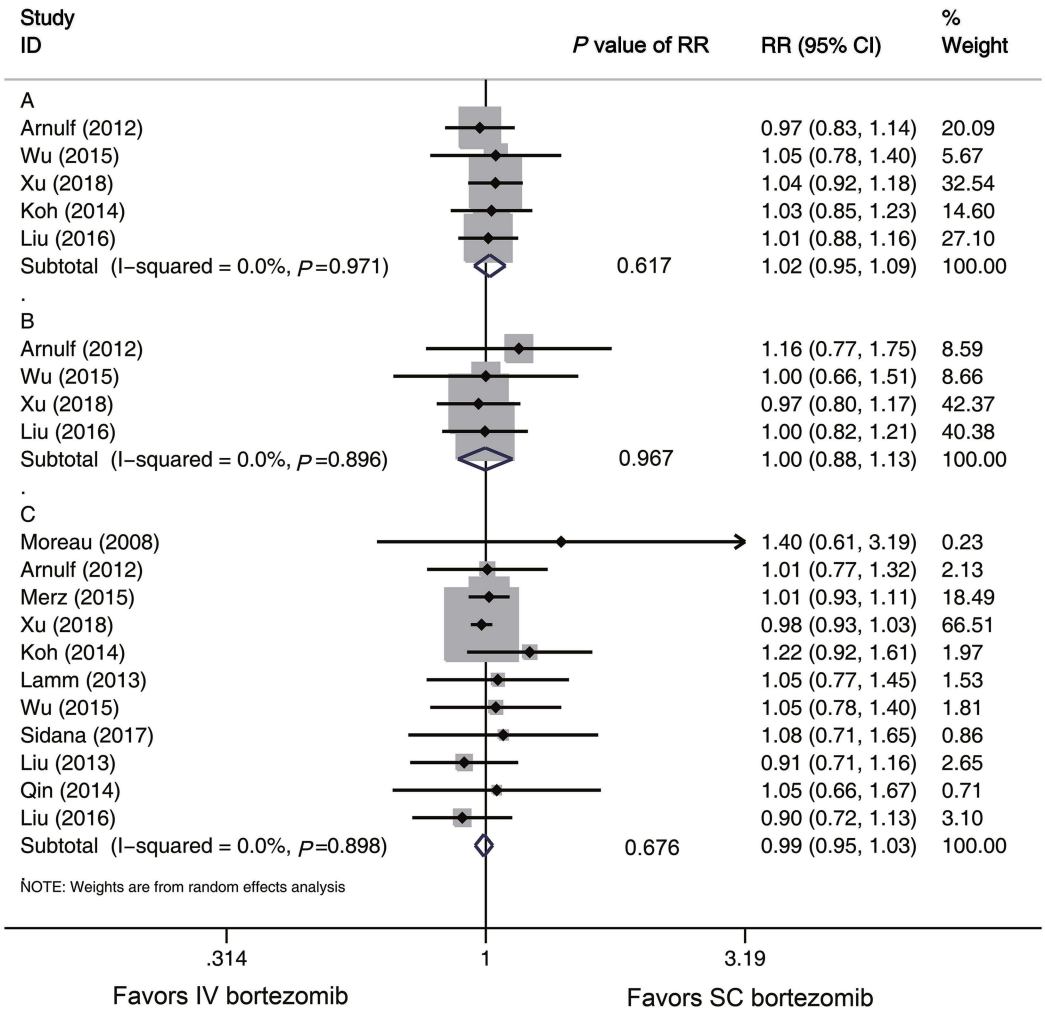

Figure 2 Annotated forest plot for meta-analysis of 1-year OS, 1-year PFS, ORR of SC and IV bortezomib. Summary of 1-year OS (**A**), 1-year PFS (**B**), ORR (**C**) risk ratio between SC and IV bortezomib were calculated using the random effect model. Size of squares is directly proportional to the amount of information available.
Abbreviations: OS, overall survival; PFS, progression-free survival; ORR, objective response rate; P, *p*-value of the Q test for heterogeneity.

I^2=0%), and 0.59 (95% CI: 0.38, 0.92, I^2=60.8%). The results showed that SC bortezomib had a significant lower incidence of the above all-grade and grade 3–4 AEs compared to IV administration of bortezomib (p<0.05). Even so, the results showed no statistical difference from other related all-grade and grade 3–4 AEs listed in Table 2 between SC and IV bortezomib arms (p>0.05).

Sensitivity analysis

The results showed that no particular study affected the overall significance of the pooled estimates, and the results of the meta-analysis were robust (Figure 3).

Publication bias

The shape of the funnel plot did not display any evidence of apparent asymmetry. Furthermore, the formal tests also showed no substantial publication bias (p=0.222 for the Egger's test; p=0.626 for the Begg's test) (Figure S1).

Discussion

The increasing interest from oncologists and patients in identifying the optimal administration route of bortezomib has been driven mainly by concerns regarding the efficacy and toxicity.[23–26] In phase III trials analyzed both for relapse cases[12] and for the newly diagnosed MM patients,[15] SC bortezomib was equally effective as the IV administration route and was associated with a reduction in the rate of peripheral neuropathy. The results of a pharmacokinetic study showed that SC bortezomib had a similar AUC (155 vs 151 ng·h/ml), but lower Cmax (20.4 vs 223 ng/mL) and longer Tmax (30 vs 2 mins)

Table 2 Meta-analysis results of the associations between bortezomib treatment and adverse events in MM patients

Grade	Adverse events	N	RR (95% CI)	*p*-Values	Test for heterogeneity		
					Chi^2	P_h	I^2
All-grade	Peripheral sensory neuropathy*	10	0.72(0.62,0.84)	<0.001	10.44	0.316	13.8%
	Diarrhea	6	0.84(0.52,1.35)	0.462	14.63	0.012	65.8%
	Leukopenia*	6	0.77(0.60,0.99)	0.043	15.76	0.008	68.3%
	Pyrexia	4	0.99(0.61,1.60)	0.954	1.24	0.744	0%
	Nausea/Vomiting	5	0.78(0.60,1.01)	0.058	2.52	0.641	0%
	Asthenia*	3	0.85(0.72,1.00)	0.044	1.23	0.539	0%
	Weight decreased	3	1.44(0.28,7.52)	0.663	5.03	0.081	60.3%
	Constipation	6	0.82(0.63,1.07)	0.145	4.86	0.433	0%
	Fatigue*	5	0.65(0.51,0.83)	<0.001	5.49	0.241	27.1%
	Infection*	3	0.64(0.46,0.89)	0.007	1.71	0.425	0%
	Pneumonia	2	0.76(0.35,1.66)	0.491	0.33	0.563	0%
	Renal and urinary disorders	3	0.50(0.24,1.04)	0.066	2.63	0.268	24.1%
	Hepatobiliary disorders*	2	0.53(0.35,0.81)	0.004	0.17	0.681	0%
	Neuralgia	3	0.95(0.59,1.53)	0.828	1.17	0.556	0%
	Anaemia	7	0.84(0.65,1.08)	0.167	16.28	0.012	63.1%
	Neutropenia	4	0.88(0.74,1.05)	0.168	1.04	0.791	0%
	Thrombocytopenia*	8	0.68(0.50,0.94)	0.018	20.22	0.003	70.3%
Grades 3–4	Peripheral sensory neuropathy*	10	0.36(0.25,0.52)	<0.001	3.71	0.883	0%
	Diarrhea*	6	0.37(0.20,0.72)	0.003	1.34	0.854	0%
	Leukopenia*	6	0.41(0.28,0.62)	<0.001	5.56	0.351	10.1%
	Pyrexia	4	0.24(0.01,4.78)	0.348	0.00	NA	NA
	Nausea/Vomiting	5	0.76(0.32,1.82)	0.535	0.48	0.787	0%
	Asthenia	3	0.49(0.20,1.21)	0.123	0.21	0.901	0%
	Weight decreased	3	0.17(0.01,4.10)	0.274	0.00	NA	NA
	Constipation*	6	0.27(0.10,0.73)	0.010	0.74	0.946	0%
	Fatigue*	5	0.45(0.23,0.85)	0.014	0.61	0.895	0%
	Infection	4	0.58(0.22,1.58)	0.289	14.86	0.002	79.8%
	Pneumonia	2	0.67(0.24,1.86)	0.444	0.00	NA	NA
	Renal and urinary disorders	4	0.49(0.20,1.19)	0.114	1.09	0.780	0%
	Hepatobiliary disorders	2	0.45(0.10,1.95)	0.284	0.81	0.370	0%
	Neuralgia*	3	0.36(0.13,0.97)	0.043	0.00	0.998	0%
	Anaemia	7	0.75(0.43,1.30)	0.299	12.15	0.059	50.6%
	Neutropenia	5	0.80(0.56,1.15)	0.233	4.13	0.388	3.2%
	Thrombocytopenia*	8	0.59(0.38,0.92)	0.019	17.87	0.013	60.8%

Note: *Statistically difference between two arms.
Abbreviations: MM, multiple myeloma; RR, risk ratio; N, number of studies; NA, not available; Ph, *p*-value of the Q test for heterogeneity.

compared to IV bortezomib.[27] The difference of pharmacokinetic parameters might be a reason why SC bortezomib had a similar efficacy but better tolerated than the IV route of administration. SC bortezomib is also more convenient and less time-consuming to the patient and institution.[28] But until now, the results from clinical trials are not compelling enough to support any definitive conclusions about the superiority of SC bortezomib. Here, we performed a systematic review and meta-analysis on the efficacy and safety of SC and IV bortezomib in both newly diagnosed and relapsed MM patients, based on 4 RCTs and 8 retrospective trials which included total 1,857 MM patients. Our results indicated that 1) there was no statistical difference in 1-year OS, 1-year PFS and ORR between SC and IV bortezomib; 2) SC bortezomib had a significantly lower incidence of all-grade peripheral sensory neuropathy, leukopenia, asthenia, fatigue, infection, hepatobiliary disorders, thrombocytopenia than IV administration route, but there was no statistical difference in risk of all-grade diarrhea, pyrexia, nausea/vomiting,

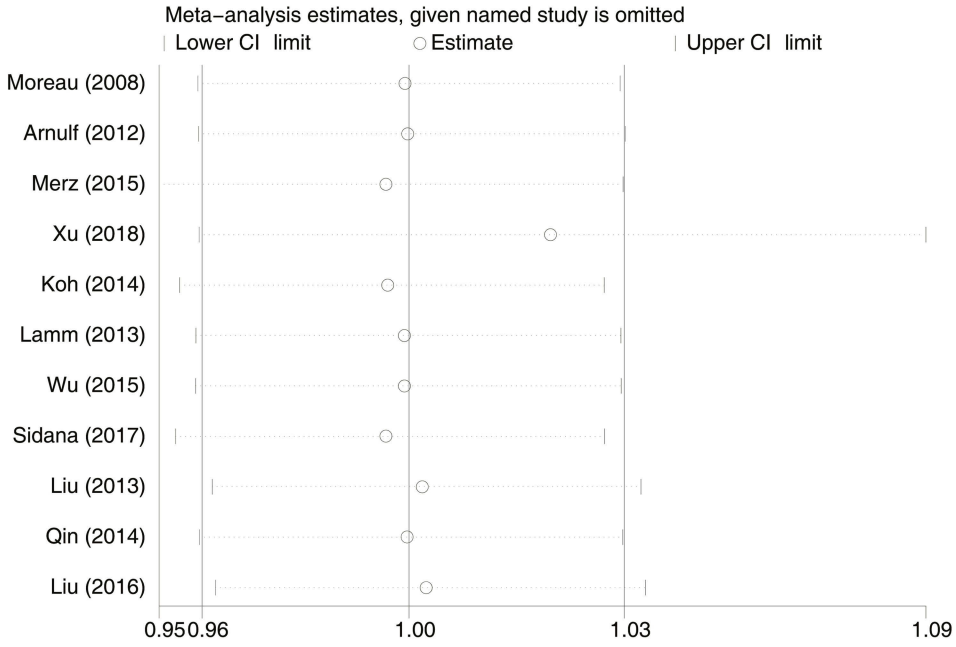

Figure 3 Sensitivity analysis of all clinical trials included.

weight decrease, constipation, pneumonia, renal and urinary disorders, neuralgia, anemia and neutropenia; 3) SC bortezomib had a significantly lower incidence of grade 3–4 peripheral sensory neuropathy, diarrhea, leukopenia, constipation, fatigue, neuralgia and thrombocytopenia than IV administration route, but there was no statistical difference in risk of grade 3–4 pyrexia, nausea/vomiting, asthenia, weight decrease, infection, pneumonia, renal and urinary disorders, hepatobiliary disorders, anemia and neutropenia.

The results of our study are partly in agreement with those performed by Mu et al[7]. In that meta-analysis, it was found that SC bortezomib had similar efficacy, lower incidence of peripheral neuropathy and thrombocytopenia to IV administration route of bortezomib. Nontheless, some studies are only abstract; the outcomes of efficacy were only ORR, and one trial included[6] was different from other trials (in one trial SC bortezomib was administered once a week, but others were twice a week), and these might affect the final results. Until now, the results of studies published for comparing the efficacy and safety of SC and IV bortezomib in MM patients remain uncertain. Our study compared the efficacy and safety of the two administration routes, and a meta-analysis was performed to draw more comprehensive results. Our study included more relevant articles, and although the number of the trials was still small, our findings might stimulate further investigations.

OS, PFS and ORR are the most important outcomes for evaluating the efficacy of treatments. The results of the meta-analysis for the patients with on-study 1-year OS, 1-year PFS and ORR showed no evidence of a significant difference between SC and IV bortezomib arms ($p>0.05$). SC administration results in equivalent bortezomib plasma exposure (such as mean AUC) to IV infusion. This pharmacokinetic study of SC and IV bortezomib might partly explain the results of similar efficacy between two administration routes arms.[27]

Another potential benefit of SC bortezomib would be the reduction of the frequencies of AEs and toxicity. The individual studies suggested that bortezomib was associated with peripheral neuropathy, nausea/vomiting, diarrhea, anemia, thrombocytopenia and leukopenia.[29–31] Peripheral nerve damage is one of the most significant nonhematologic toxicities of bortezomib. The painful sensory neuropathy elicits most concerns by clinicians, which not only seriously affect the quality of life of patients, but also one of the reasons for the non-compliance to treatment.[32–34] Overall, it appears that SC bortezomib caused a significantly lower incidence of peripheral neuropathy compared to IV administration, in both all-grade and grade 3–4 ($p<0.001$). The results of this systematic review also suggested that SC bortezomib caused a significantly lower incidence of some AE, such as leukopenia and thrombocytopenia, which indicated that SC bortezomib might be a better choice for some patients with higher AE risk factors.

Heterogeneity was an important concern in the meta-analysis. The heterogeneity might not be totally ruled out in this study, and so the sensitivity analysis was used to identify the robustness of our findings. The results displayed that no study affected the overall significance of the pooled estimates, and the results of our findings were robust. Publication bias might introduce false positives in the meta-analysis.[11] To avoid the possible bias, the studies included were all properly assessed. Egger's and Begg's tests used in detecting publication bias were performed and no evident bias was found. The results of publication bias and sensitivity analysis indicated that conclusions of our study are credible.

The following limitations merit consideration, and hence, the present meta-analysis should be interpreted with caution. First, there were few studies, especially due to the lack of sufficient high-quality RCTs. Second, although the dosage and schedule of the two drugs in all trials included were consistent, additional rigorously designed experiments are required. Third, the trials included in our analysis were open label, which might affect the outcomes.

Conclusion

In summary, compared to IV administration, SC bortezomib showed equivalent efficacy but caused a significantly lower incidence of some all-grade or grade 3–4 AEs, such as peripheral sensory neuropathy, leukopenia and thrombocytopenia. The data presented so far has consistently shown that SC bortezomib has become a standard of care for patients with MM.

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Disclosure

The authors report no conflicts of interest in this work.

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Supplementary material

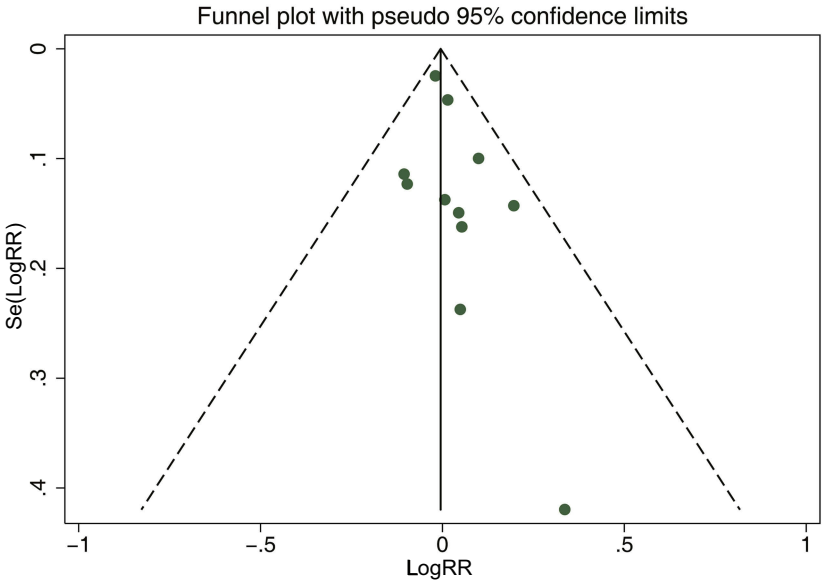

Figure S1 Publication bias risk.
Abbreviations: RR, risk ratio; s.e., standard error of the mean.