European Journal of Internal Medicine 69 (2019) 32–41

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Original Article

The efficacy and safety of bortezomib-based chemotherapy for immunoglobulin light chain amyloidosis: A systematic review and meta-analysis

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ARTICLE INFO

Keywords:
AL amyloidosis
Bortezomib
Meta-analysis
Chemotherapy

ABSTRACT

Background: The role of bortezomib in the treatment of immunoglobulin light chain (AL) amyloidosis is not well defined. We performed this meta-analysis to evaluate the efficacy and safety of bortezomib-based regimens in patients with AL amyloidosis who are not eligible for or refuse autologous stem cell transplantation.

Methods: A systematic search of Medline, Embase, and the Cochrane Library was conducted to identify related studies.

Results: Twenty-four studies with 1238 patients were included. The pooled overall response rate (ORR) and complete hematological response rate (CHR) were 0.72 (95% CI, 0.67–0.77) and 0.35 (95% CI, 0.30–0.40), respectively. Bortezomib significantly improved the outcome of ORR compared to other regimens (RR 1.28, 95% CI, 1.04–1.57, $P = .02$). Similar results were observed in CHR (RR 1.90, 95% CI, 1.45–2.50, $P < .001$) and cardiac response (RR 2.03, 95% CI, 1.31–3.13, $P = .002$), but not in overall survival (HR 0.82, 95% CI, 0.62–1.09, $P = .17$). In addition, once-weekly bortezomib was associated with improved overall survival compared with twice-weekly bortezomib (HR 0.52, 95% CI, 0.27–0.99, $P = .05$). Peripheral neuropathy was the most widely reported adverse event. Incorporation of bortezomib into the standard melphalan + dexamethasone setting showed a trend of increased serious adverse events, though this was not statistically significant (RR 1.29, 95% CI, 0.95–1.75, $P = .10$).

Conclusions: Current evidence indicates that bortezomib-based regimens might be effective and safe therapies for patients with AL amyloidosis. There is a great need to conduct more well-designed randomized controlled trials to provide high-quality evidence.

1. Introduction

Immunoglobulin light chain (AL) amyloidosis is a systematic disease characterized by deposition of misfolded immunoglobulin light chains derived from monoclonal plasma cells, which can lead to multi-organ dysfunction [1]. It is the most common type of amyloidosis with a prevalence between 8.8 and 58 individuals per million person-years [2] and an annual percentage increase of 12% [3]. Although rare, AL amyloidosis is associated with high mortality in affected individuals. It was reported that before 1993, the median survival was 13.2 months, and only 7% of the patients survived for 5 or more years if they did not receive effective treatment [4]. With the development of autologous stem cell transplantation (ASCT) and novel agents such as thalidomide and bortezomib, the overall survival (OS) has largely been improved. However, 4-year OS remains low at 50%, and early mortality remains high [5]. This has led to serious damage, not only physiologically but also psychologically [6], and has put severe economic burdens on society [7].

Bortezomib, a reversible inhibitor of the 26S proteasome, was developed with the aim of treating multiple myeloma (MM) by inhibiting proliferation and inducing apoptosis in human MM cell lines [8]. Due to its high response rates in MM, bortezomib was introduced for AL amyloidosis at the American Society of Hematology Annual Meeting in 2006 by Wechalekar et al. [9]. Recently, there has been an increased interest in using bortezomib to treat patients with AL amyloidosis. However, the strong evidence to prove its exact role in AL amyloidosis

Abbreviations: AL, immunoglobulin light chain amyloidosis; ASCT, autologous stem cell transplantation; OS, overall survival; MM, multiple myeloma; AE, adverse events; CHR, complete hematological response rate; ORR, overall response rate; QW, once weekly; BIW, twice weekly.

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https://doi.org/10.1016/j.ejim.2019.08.011
Received 16 June 2019; Received in revised form 3 August 2019; Accepted 13 August 2019
Available online 22 August 2019

is yet unavailable. Patients' current treatment is based on expert consensus rather than the evidence of prospective clinical trials. Whether bortezomib can improve response rates or OS remains controversial. In particular, one editorial summarized two matched series that compared bortezomib-based regimens to those without for treating AL amyloidosis and concluded there was no certainty about the role of bortezomib [10].

Although one meta-analysis [11] has reported the effect of bortezomib in patients with AL amyloidosis, there was no strong evidence to prove that bortezomib could improve overall survival because they employed dichotomous data to evaluate the pooled effects of two-year OS and overall mortality, which would lead to a loss of censored information. The small sample size and a lack of detailed description of toxicities also limit the interpretation of that meta-analysis. Furthermore, they took patients who were eligible for ASCT into account. Our present meta-analysis aims to evaluate the efficacy and safety of bortezomib in AL amyloidosis patients who are not eligible for or refuse ASCT, in contrast the above meta-analysis.

2. Materials and methods

2.1. Search strategy

We searched the Medline (PubMed), Embase (Ovid), and Cochrane Library databases from inception to 22 June 2018 by a combination of Medical Subject Heading terms and keywords to identify studies assessing bortezomib in the setting of AL amyloidosis. The detailed search strategy is listed in Supplementary Materials. We also searched ClinicalTrials.gov for unpublished results and manually reviewed the references of relevant articles.

2.2. Study selection

The included studies met the following eligibility criteria: (1) AL amyloidosis patients were treated with bortezomib; (2) the study reported the details of the application of bortezomib; and (3) the study reported the overall response rate (ORR). Studies meeting any of the following criteria were excluded: (1) it had fewer than 5 patients; (2) bortezomib was used for induction therapy before or after ASCT; (3) any patient had MM-associated AL amyloidosis; (4) bortezomib was combined with other novel agents (such as lenalidomide, pomalidomide, doxycycline, and monoclonal antibodies for amyloid deposits or plasma cells). When more than one study reported the results from the same cohort, only the most recent study was included. Full-text review was restricted to Chinese and English articles only.

2.3. Data extraction

Two of our authors (Baojian Liu and Ming Bai) independently extracted the data from each primary study with a predefined form: first author and year of publication, study design, demographics, details of using bortezomib, outcomes, and adverse events (AEs). The quality of the included studies was assessed using the Newcastle-Ottawa Scale, which ranges from zero (lowest quality) to nine points (highest quality) [12]. Disagreements were resolved by discussion and consensus. The primary outcome of interest was ORR. Secondary objectives included complete hematological response rate (CHR), OS, organ response, and AEs.

2.4. Statistical analysis

Risk ratios (RRs) with 95% confidence intervals (CIs) were pooled for dichotomous data. Hazard ratios (HRs) were pooled for time-to-event data. Observed minus Expected events (*O-E*) and Variance (*V*) were calculated using the HR with its 95% CI, observed events, the number of analysed patients, and the *P* value of the log-rank test. In the absence of these variables, the survival curves were used to estimate the *O-E* and *V*, employing the calculation spreadsheet provided by Tierney et al. [13]. Heterogeneity was measured by the chi-squared test and the I^2 statistic. A random-effect model was used if there was high heterogeneity (value of I^2 over 50%) [14]; otherwise, a fixed-effect model was used. Sensitivity analyses were used to explore the potential sources of heterogeneity.

Publication bias was assessed by funnel plot and Begg's test [15]. For the controlled studies, statistical analyses were performed using Review Manager (version 5.3, The Nordic Cochrane Centre, The Cochrane Collaboration 2011, Copenhagen, Denmark). Comprehensive Meta-Analysis software (version 2.0, Englewood, NJ, USA: Biostat Inc.; 2005) was used to pool the single-arm data and calculate the Begg's test. $P < .05$ was considered statistically significant.

3. Results

3.1. Study selection, characteristics, and quality

The systematic literature review yielded 217, 331, and 34 studies in the Medline, Embase, and Cochrane databases, respectively. After excluding 105 duplicate articles, 477 articles were left for title and abstract screening, of which 418 were excluded. The remaining 59 articles' full-texts were reviewed, and 35 articles were excluded. Notably, although one RCT was reported in the form of a conference abstract [16], considering its high-level evidence and detailed data, we incorporated it into the final analysis. Another RCT [17] was identified by retrieval from ClinicalTrials.gov and was included for the same reason. Nine were duplicate reports [18–26], and only the papers [21,24,26] with the longest follow-up for each cohort were used for analysis. Finally, 24 studies with 1238 AL amyloidosis patients were included in the final analyses, including 8 controlled studies [16,17,27–32] and 16 single-arm studies [21,24,26,33–45]. The process of study selection is presented in Fig. 1.

The basic characteristics of the included studies are presented in Tables 1 and 2. These 24 studies included 2 RCTs [16,17], 2 phase 1/2 trials [21,35], and 20 retrospective studies [24,26–34,36–45]. The mean age of patients ranged from 54 to 69 years. The median number of cycles received of bortezomib was 3.6 (range 2.0–8.0) in a median

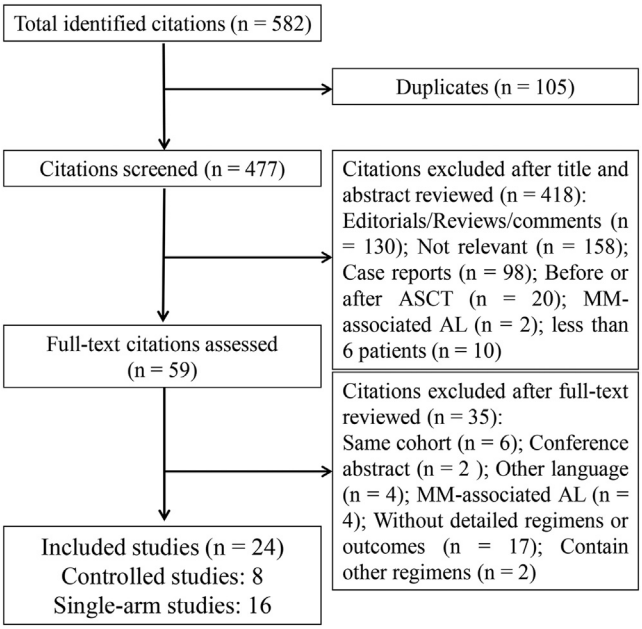

Fig. 1. Study inclusion flowchart. ASCT, autologous stem cell transplantation; MM, multiple myeloma.

Table 1
Basis characteristics of studies with active controls.

Reference	Study type	Area	Study period	Mean age (years)	Follow-up time (m)	Organ involvement	Untreated	Bortezomib						Non-bortezomib					
								Regimen	N	ORR	Survival	TTR(m)	Cycles	Regimen	N	ORR	Survival	TTR(m)	Cycles
Katoh 2017 [27]	R/S	Japan	2001–2016	63	NA	H: 40%, K: 80%, L: 15%	BD:65% ASCT:100%	BD	20	90%	Median:NR	NA	3.3	ASCT	30	73%	Median:NR	NA	NA
Feng 2017 [28]	R/S	China	2009–2016	NA	NA	H: 100%	NA	CBD/BD	16	58%	NA	1.0	3.0	M/T/L	8	38%	NA	6.0	NA
Kastritis 2016 [16]	RCT/M	Europe/ Australia	2011–2016	59	25	H: 77%, K: 68%, L: 13%	100%	BMD	53	81%	Median:NR	NA	5.0	MD	57	56%	Median:NR	NA	5.0
Sayago 2016 [29]	R/S	Spain	2005–2015	60	14	H: 100%	NA	BD/BMD/ CBD	23	96%	1-y:91%2-y:73%	5.1	NA	NA	8	25%	1-y:15%2-y:0%	NA	NA
Kastritis 2015 [30]	R/S	Greece	2005–2012	Full dose BD: 70; Risk adapted BD: 67	57	Full dose BD: H: 84%, K: 60%, L: 4% Risk adapted BD: H: 72%, K: 82%, L: 14%	100%	BD	49	77%	1-y:67%4-y:43%	1.3	NA	LCD	36	58%	1-y:53%4-y:53%	4.5	NA
Venner 2014 [31]	R/S	UK	2008–2012	60	13	H: 81%, K: 75%, L: 30%	100%	CBD	69	71%	Median:NR 1-y:65%	1.2[a]; 2.2[b]	3.7	CTD	69	80%	Median:NR 1-y:67%	1.0[a]; 2.8[b]	3.8
Palladini 2014 [32]	R/S	Italy	2005–2012	69	26	H: 85%, K: 63%, L: 10%	100%	BMD	87	69%	Median:NR	1.1[a]	4.0	MD	87	51%	Median: 30 mo	1.4[a]	3.0
Dispenzieri 2014 [17]	RCT/M	USA	2010–2014	66	NA	NA	100%	BMD	5	60%	NA	NA	3.0	MD	6	33%	NA	NA	3.0

R: retrospective study; P: prospective study; S: single-centre; M: multi-centre; RCT: randomized controlled trial; NA: not available; NR: not reached; ORR: overall response rate; TTR: time to response; H: heart involvement; K: kidney involvement; L: liver involvement.

ASCT: autologous stem cell transplantation; BD: bortezomib + dexamethasone; CBD: cyclophosphamide + bortezomib + dexamethasone; BMD: melphalan + bortezomib +dexamethasone; MD: melphalan + dexamethasone; LCD: lenalidomide + cyclophosphamide + dexamethasone; CTD: cyclophosphamide + thalidomide + dexamethasone; M/T/L: melphalan/thalidomide/lenalidomide.

[a] First response.

[b] Best response.

Table 2
Basis characteristics of single-arm studies.

Reference	Study type	Area	Study period	Mean age (years)	Follow-up time(m)	Organ involvement	Untreated	Regimen	N	ORR	Survival	TTR(m)	Cycles
Kastritis 2017 [34]	R/S	Greece	BD: 2005–2010 CBD: 2011–2013	BD:67 CBD: 61	36	BD: H:70%, K: 75% CBD: H:71%, K: 66%	100%	BD/CBD	BD:59,CBD:42	BD:68% CBD:78%	BD: 33 mo CBD: 36 mo	BD:median:1.2[a]; CBD:median:1.3[a]	NA
Shen 2017 [33]	R/S	China	2009–2017	57	12	H:79%, K: 71%, L: 16%	100%	CBD/BD	89	75%	Median: NR 2-y:72%, 3-y:62%	1.0[a]; 2.0[b]	NA
Jimenez-Zepeda 2016 [36]	R/S	Canada	2009–2015	64	20	H:71%, K: 71%, L: 10%	81%	CBD/BD/ BMD	52	94%	Median: NR	NA	4.0
Huang 2016 [37]	R/S	China	2009–2014	57	24	H:72%, K: 100%, L: 19%	100%	BD	72	75%	Median: NR 1-y:83%, 2-y:76%	2.0	2.0
Shimazaki 2016 [35]	P/M	Japan	2011–2014	55	27	H:11%, K: 78%, L: 33%	0%	BMD	9	78%	NA	NA	4.0
Palladini 2015 [38]	R/M	UK/Italy	2006–2013	60	25	H:73%, K: 68%, L: 11%	100%	CBD	230	60%	3-y:55%	NA	4.0
Huang 2015 [26]	R/S	China	2006–2012	63	23	H:75%, K: 100%, L: 50%	100%	BD	12	80%	NA	1.0	3.5
Reece 2014 [21]	P/M	Canada/France/ Germany/Italy/ Spain/USA	2005–2012	61	52	H:56%, K: 73%, L: 13%	0%	B	70	60%	Median: 63 mo 4-y:67%	QW:2.1[a]; 3.2[b] BIW:0.7[a]; 1.2[b] Low-dose:1.2[a]; 1.2[b]	QW:8.0 BIW:6.0 Low-dose:8.0
Jaccard 2014 [39]	R/M	USA/UK/France	2008–2012	66	12	H:100%, K: 57%, L: 20%	100%	CBD	60	68%	Median: NR,1-y:57%	2.1[b]	3.0
Lu 2013 [40]	R/S	China	2008–2012	56	7	H:90%	41%	CBD	22	64%	Median: 6 mo	1.0	2.0
Venner 2012 [41]	R/S	UK	2006–2011	54	14	H:74%, K: 79%, L: 23%	47%	CBD	43	81%	2-y:98%	4.1[b]	5.0
Mikhael 2012 [42]	R/S	USA	2007–2010	NA	21	H:58%, K: 82%, L: 24%	59%	CBD	17	94%	NA	2.0	3.0
Lamm 2011 [43]	R/M	Austria	2006–2009	62	15	H:35%, K: 100%, L: 15%	69%	BD	26	54%	Median: 19 mo	1.8	3.0
Coriu 2011 [44]	R/S	Romania	2008–2010	55	8	H:88%, K: 63%, L: 38%	38%	B/BD	8	75%	NA	1.5	3.5
Zhai 2010 [45]	R/S	China	2007–2009	55	6	H:46%, K: 100%, L: 55%	64%	BD	11	36%	Median: NR	2.0	3.0
Kastritis 2010 [24]	R/M	Greece/UK/Italy	NA	62	12	H:73%, K: 75%, L: 19%	19%	B/BD	94	72%	Median: NR 1-y:76%	1.7	4.0

R: retrospective study; P: prospective study; S: single-centre; M:multi-centre; RCT: randomized controlled trial; NA: not available; NR: not reached; ORR: overall response rates; TTR: time to response; H: heart involvement; K: kidney involvement; L: liver involvement; QW, once weekly; BIW, twice weekly.
BD: bortezomib + dexamethasone; CBD: cyclophosphamide + bortezomib + dexamethasone; BMD: melphalan + bortezomib + dexamethasone; MD: melphalan + dexamethasone; LCD: lenalidomide + cyclophosphamide + dexamethasone; CTD: cyclophosphamide + thalidomide + dexamethasone; B: bortezomib.
[a] First response.
[b] Best response.

follow-up time of 20.0 months (range 6.0–51.8). Seven studies [27,30,32,34,36,37,43] included consecutive patients. Bortezomib was given subcutaneously or intravenously with the highest dose of 1.6 mg/m^2 and the lowest dose of 0.7 mg/m^2 (Supplementary Table 1). Once-weekly (QW) bortezomib was reported in 2 studies [28,33], both from China. A twice-weekly (BIW) schedule was executed in eleven studies, and other studies combined the two schedules.

The quality of each study is presented in Supplementary Table 2. We defined two years as a sufficient follow-up time. The inclusion of non-exposed cohorts and comparison groups was not suitable for single-arm studies. None of them received the highest score. We did not score the two RCTs by the Jadad scale because they were not reported in the full text. Overall, the methodological quality was poor.

4. Outcomes

4.1. Hematological response

All of the studies could be used to evaluate ORR. The pooled ORR was 0.72 (95% CI, 0.67–0.77), with range from 0.36 [45] to 0.96 [29], and there was a significant inter-trial heterogeneity (I^2 = 59%, P < .001, Fig. 2A). Sensitivity analysis excluding the studies with fewer than 40 patients did not change the significant heterogeneity (I^2 = 65%, P = .001), and the pooled ORR of the remaining studies was 0.73 (95% CI, 0.68–0.77). The funnel plot showed a symmetric distribution, and Begg's test indicated that there was no significant publication bias in the total-group analysis (P = .09, Supplementary Fig. 1A). Data on CHR were reported in 22 studies, which excluded the two RCTs, and the CHR ranged from 0.17 [39] to 0.71 [42]. The pooled proportion of CHR was 0.35 (95% CI, 0.30–0.40), with significant heterogeneity (I^2 = 65%, P < .001, Fig. 2B). Subgroup analyses were performed according to the treating history, the frequency of using bortezomib, and the number of combined drugs (Supplementary Table 3). The results indicated that the frequency of using bortezomib may have been the source of the heterogeneity.

There were 8 studies with active control reporting ORR. The pooled RR was 1.28 (95% CI, 1.04–1.57, P = .02, Fig. 3A), significantly favouring bortezomib-based regimens. However, the inter-trial heterogeneity was significant (I^2 = 61%, P = .01). Sensitivity analyses were performed by excluding the 6 retrospective studies and the 4 studies [17,28,29,34] that had small samples (fewer than 40 patients). No significant heterogeneity (I^2 = 0%, P = .75) and a superior ORR in the bortezomib group (RR 1.46, 95% CI, 1.13–1.90, P = .004) were observed in the two RCTs (Supplementary Fig. 2A). The large number of patients in individual studies could not reduce the heterogeneity (I^2 = 76%, P = .005, Supplementary Fig. 2B). Moreover, incorporation of bortezomib (BMD) into the standard melphalan + dexamethasone (MD) setting was related to a significantly improved ORR (RR 1.41, 95% CI, 1.17–1.69, P < .001, Supplementary Fig. 2C) according to the 3 studies that tested this [16,17,32]. Additionally, the funnel plot and Begg's test for the 8 controlled studies demonstrated a low risk of publication bias (P = .19, Supplementary Fig. 1B). For CHR, data were available in six studies with active control. The pooled results significantly favoured the bortezomib-based chemotherapies (RR 1.90, 95% CI, 1.45–2.50, P < .001, Fig. 3B), with no significant heterogeneity (I^2 = 2%, P = .40).

4.2. Overall survival

Time-to-event data were used to evaluate the OS in 6 studies. HRs and 95% CIs were used to calculate *O-E* and *V* in 2 studies [29,30], while observed events, number of analysed patients, and *P* value were used in 3 studies [16,27,32]. There were no data on the calculation of *O-E* or *V* directly in the study reported by Venner et al. [31], so we used the Kaplan-Meier curve to assess essential data. Finally, a total of 303 patients in the bortezomib group and 294 patients in the non-bortezomib group were pooled for OS, and the HR was 0.82 (95% CI, 0.62–1.09, P = .17), indicating a statically nonsignificant difference in survival benefit between the bortezomib and non-bortezomib groups (Fig. 3C). No significant heterogeneity (I^2 = 38%, P = .15) was observed. Similar results were found in untreated patients [16,30–32] (HR 0.90, 95% CI, 0.67–1.20, P = .47, Supplementary Fig. 3). For the 2 studies [16,32] that compared BMD with MD, bortezomib was also not associated with significantly improved OS (HR 0.78, 95% CI, 0.54–1.14, P = .21) in patients with AL amyloidosis. Further analysis found that if we excluded the study reported by Venner et al. [31], a significant survival advantage (HR 0.72, 95% CI, 0.53–0.99, P = .04) would occur.

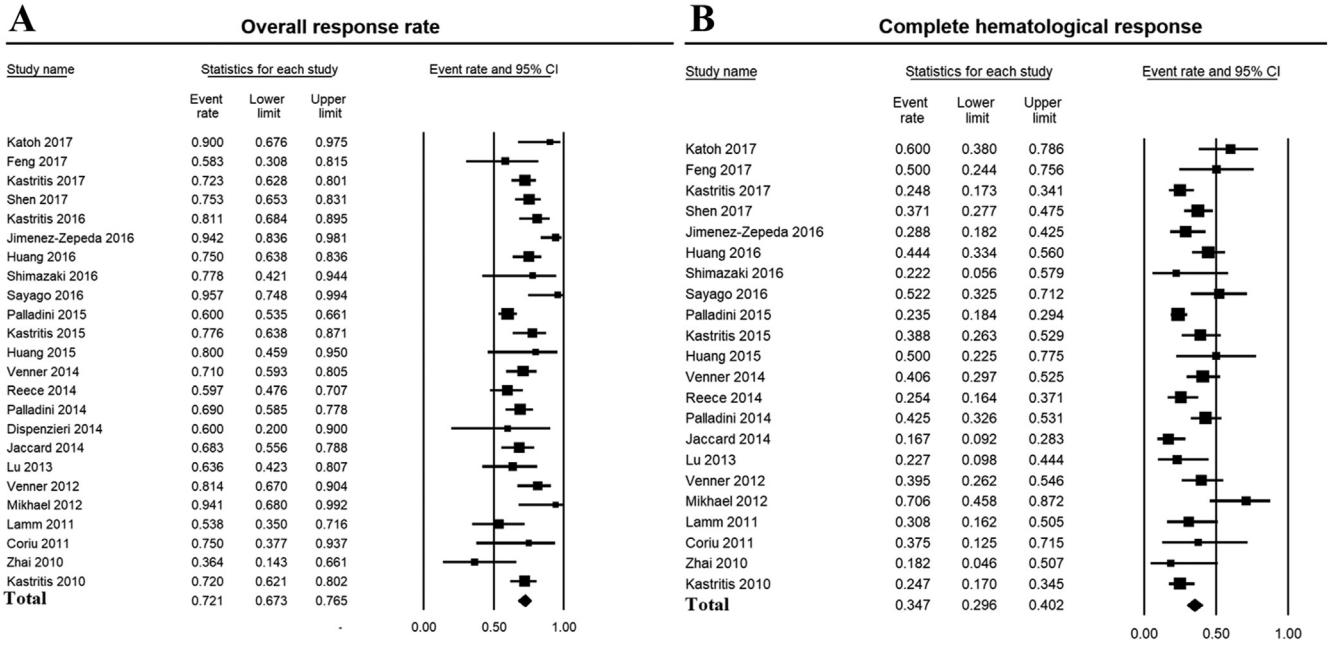

Fig. 2. Forest plot of pooled hematological response: (A), overall response rate, (B), complete hematological response.

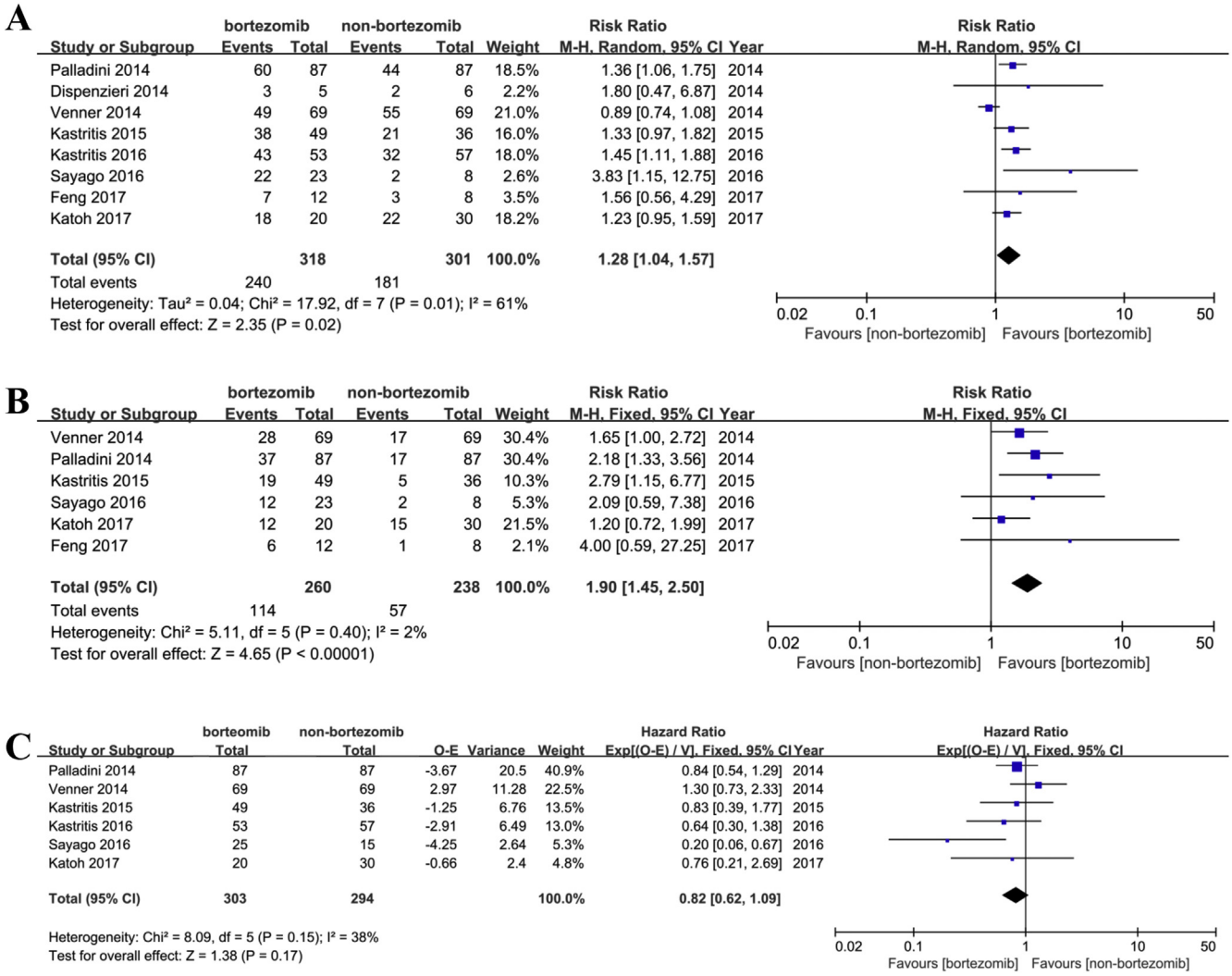

Fig. 3. Forest plot of comparisons: bortezomib versus non-bortezomib. Outcomes: (A), overall response rate, (B), complete hematological response, (C), overall survival.

4.3. Organ response

Data comparing cardiac response between bortezomib and non-bortezomib groups were extracted from 5 studies. Sixty-four of the 193 patients treated with bortezomib had a cardiac response, compared to 25 of the 163 patients with other chemotherapies. The pooled results revealed that bortezomib was associated with significantly improved cardiac response in patients with AL amyloidosis (RR 2.03, 95% CI, 1.31–3.13, $P = .002$, Fig. 4A), and no heterogeneity ($I^2 = 0\%$, $P = .43$) was detected among the included studies.

However, only 3 studies compared bortezomib with non-bortezomib on renal response, and the pooled results showed that using bortezomib did not improve renal outcome (RR 0.90, 95% CI, 0.65–1.25, $P = .54$, Fig. 4B). There was also no heterogeneity ($I^2 = 0\%$, $P = .39$). Meta-analysis was not conducted on hepatic response, as only one study reported the relevant data. Hepatic response occurred in 8 of 15 patients in the cyclophosphamide + bortezomib + dexamethasone (CBD) cohort compared to 3 of 13 patients in the cyclophosphamide + thalidomide + dexamethasone (CTD) cohort ($P = .1$) [31].

We also pooled the studies with or without active control for organ response. Cardiac response rates ranged from 0% [45] to 60% [29], renal response rates ranged from 11% [35] to 60% [37], and hepatic response rates ranged from 0% [21] to 53% [31]. The pooled results are listed in Table 3 and show that the proportions of organ response were over 30% in the setting of bortezomib.

4.4. Adverse events

Among the 24 studies, four retrospective single-centre studies [28,30,31,33] did not report any AE. Peripheral neuropathy was reported in the remaining 20 studies and was the most widely reported toxicity. Fifteen of the 20 studies reported all grades of peripheral neuropathy and were pooled for occurrence rate (32.7%, 95% CI, 25.0%–41.5%). Thirteen of the 20 studies reported serious peripheral neuropathy, and the pooled rate was 5.6% (95% CI, 2.7%–11.4%). Both of the above analyses exhibited significant heterogeneity ($I^2 = 73\%$ for 15 studies, $I^2 = 71\%$ for 13 studies). On the other hand, no patient in the non-bortezomib cohort developed peripheral neuropathy.

Hematological toxicity was reported in 10 studies. Other common AEs were infection (8), herpes zoster (6), diarrhoea (6), fatigue (6), hypotension (6), constipation (5), fluid retention (5), heart failure (5), and renal dysfunction (5). Five studies [17,21,24,44,45] reported overall toxicities of any grade, ranging from 62.5% [44] to 100% [17,45], and were pooled for analysis. The pooled proportion was 0.87 (95% CI, 0.72–0.95) with significant heterogeneity ($I^2 = 60\%$, $P = .04$). Overall, serious toxicities were reported in 6 studies [16,17,21,24,32,44], with rates ranging from 21.8% [32] to 61.4% [21], and the pooled result was 0.43 (95% CI, 0.27–0.61), with

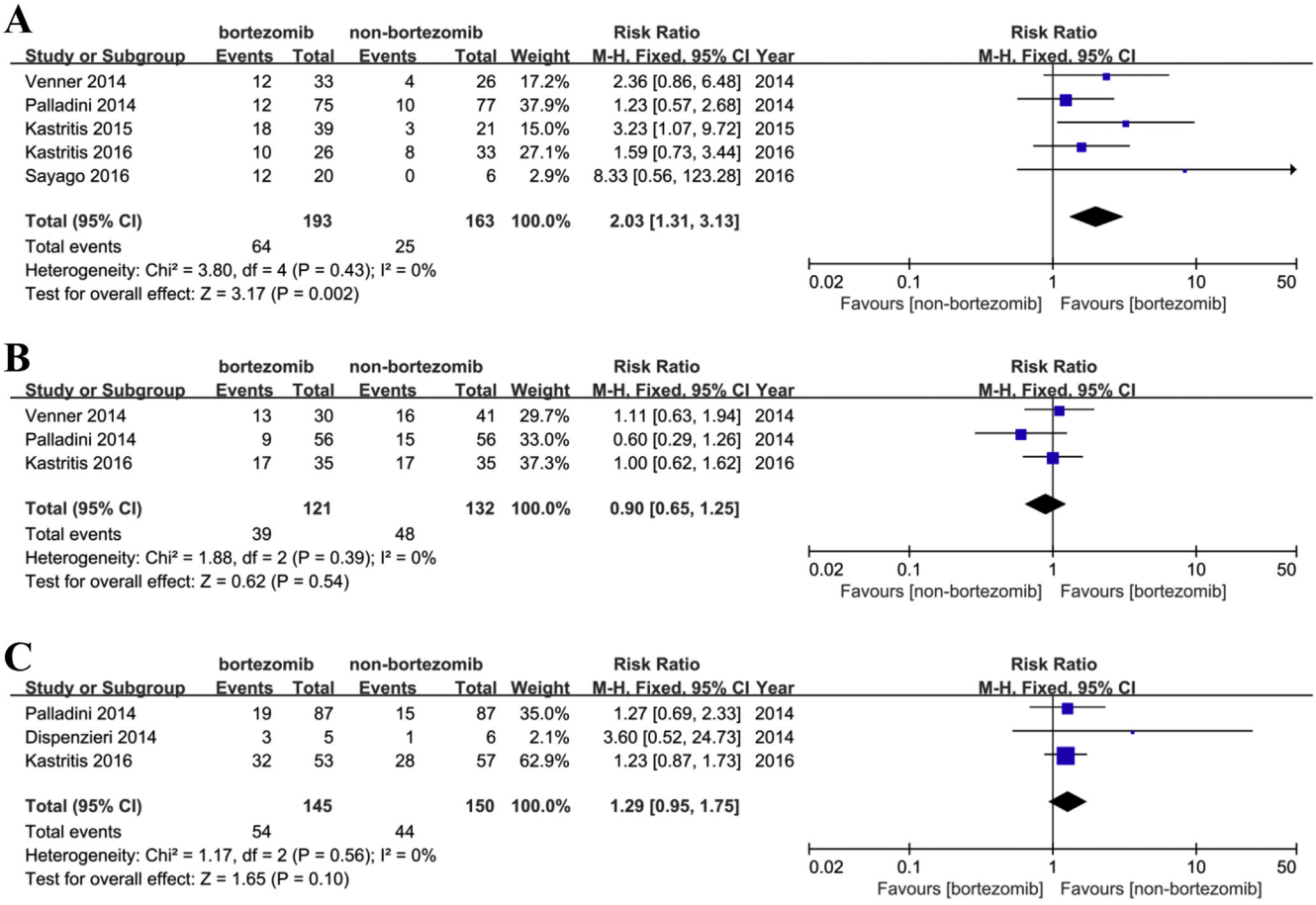

Fig. 4. Forest plot of comparisons: bortezomib versus non-bortezomib. Outcomes: (A), cardiac response, (B), renal response, (C), serious adverse events.

Table 3
Pooled organ response.

Organ	Studies	Response rates (95% CI)	I^2	*P* for heterogeneity
Kidney	15	0.351(0.276–0.435)	74.3%	< 0.001
Heart	15	0.312(0.244–0.390)	74.8%	< 0.001
Liver	10	0.328(0.249–0.419)	0%	0.545

significant heterogeneity (I^2 = 87%, P < .001).

Only 3 studies [16,17,32] compared bortezomib with other regimens on overall serious toxicities. In total, 54 of the 145 patients in the bortezomib group had serious toxicities, compared to 44 of the 150 patients in the non-bortezomib group. The pooled RR was 1.29 (95% CI, 0.95–1.75, P = .10), with no heterogeneity (I^2 = 0%, P = .56). Although this difference was not statistically significant, there was a trend towards increased serious AEs from the triple combination (Fig. 4C). The detailed bortezomib-based regimen-associated AEs are listed in Supplementary Table 4.

4.5. Other outcomes

We further investigated the efficacy of QW and BIW bortezomib in patients with AL amyloidosis. Data were extracted from 6 and 3 studies for comparing QW and BIW bortezomib on ORR and CHR, respectively. The results revealed that increased frequency of bortezomib was not associated with improved hematological response rate (RR 0.89, 95% CI, 0.77–1.04, P = .15 for ORR; RR 0.80, 95% CI, 0.43–1.49, P = .49 for CHR; Fig. 5A and 5B). However, for time-to-event data, the pooled HR of the 3 studies indicated that QW led to an improvement in survival (HR 0.52, 95% CI, 0.27–0.99, P = .05, Fig. 5C). Notably, in the pooled results, the number of patients using BIW bortezomib was about twice the number of patients using QW bortezomib.

History of treatment (untreated vs pretreated) was also compared for ORR. Six studies were analysed and the results showed that primary-setting patients were more prone to respond to bortezomib than recurrent- or refractory-setting patients (RR 1.23, 95% CI, 1.03–1.45, P = .02, Supplementary Fig. 4).

5. Discussion

Our meta-analysis revealed that bortezomib-based regimens could offer reasonable ORR, CHR, and organ response in patients with AL amyloidosis. Furthermore, bortezomib was able to improve ORR, CHR, and cardiac response compared with other regimens. However, pooled analysis showed no difference in OS between bortezomib and non-bortezomib groups due to some potential limitations. Additionally, treatment of AL amyloidosis with QW bortezomib seemed to be associated with higher OS but without improved ORR and CHR.

We performed this meta-analysis on 24 studies, of which 8 studies compared bortezomib with other regimens. Together, this review included a total of 1228 AL amyloidosis patients treated with bortezomib and 301 patients with other therapies as a control. Our study showed a pooled ORR of 72.1% and a pooled CHR of 34.7%, higher than most of the data previously reported in ASCT trials [46]. The survival time was shorter in the bortezomib groups than in the ASCT trials. However, ASCT and bortezomib were reported in different settings with limited comparability. In our study, compared with other therapies, bortezomib was associated with higher ORR, CHR, and cardiac response in patients with AL amyloidosis, all of which have been validated to be important prognostic risk factors for survival [47].

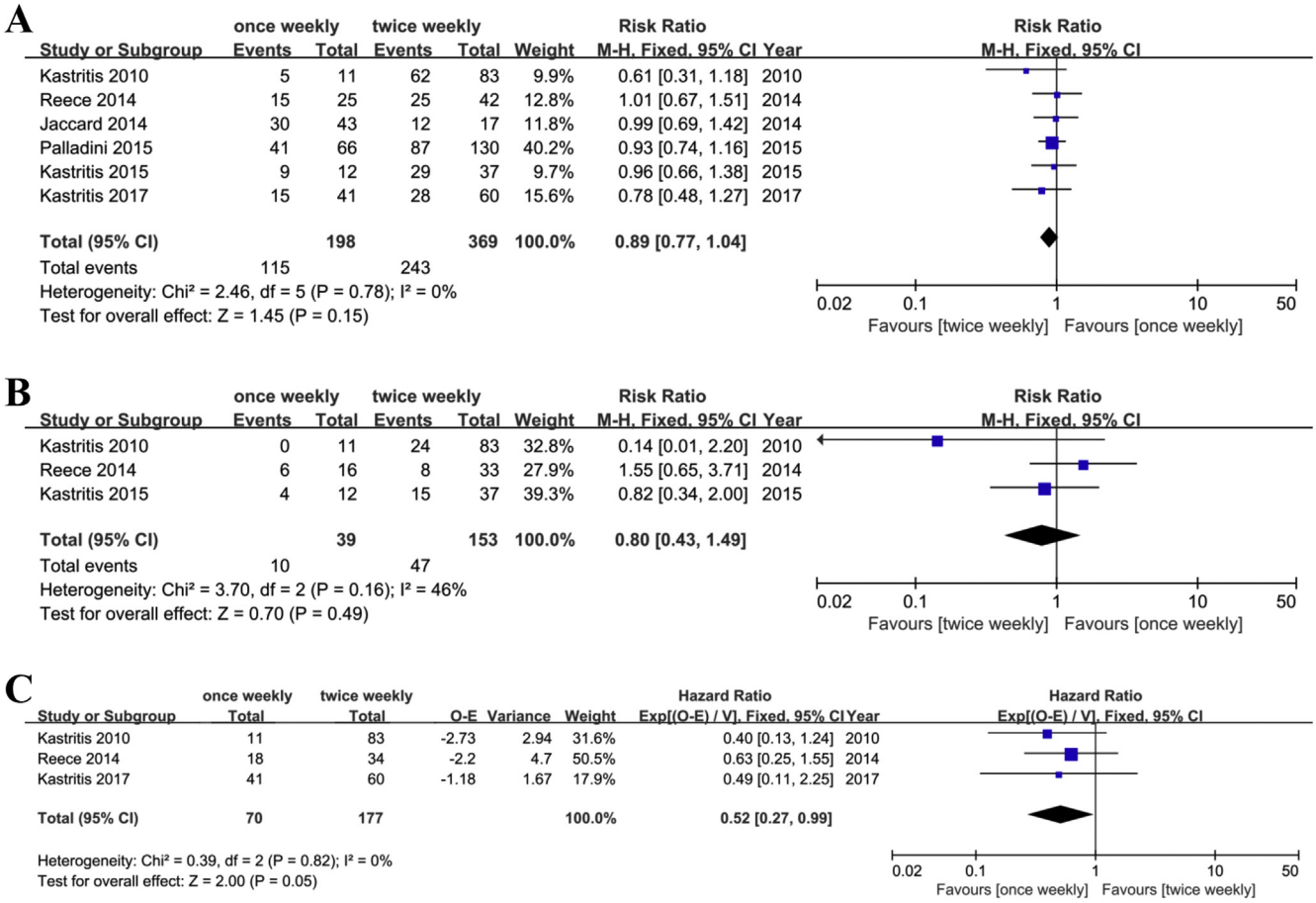

Fig. 5. Forest plot of comparisons: once weekly versus twice weekly. Outcomes: (A), overall response rate, (B), complete hematological response, (C), overall survival.

According to the PRISMA statement, HR is the optimum measure to pool time-to-event data because it takes both the number of events and the time to event into account [13,48]. Therefore, we polled HRs of the survival to present more reliable results. No survival benefit was confirmed in our study. The small sample size, short follow-up time (median 25.0 mo, range 12.7–57.0 mo for the 8 controlled studies), different incidence of AEs in the two groups, and loss of data in some studies may account for this perplexing phenomenon. Notably, we found that one study was not consistent with the other five studies in survival tendency, and if we removed it from the analysis, bortezomib would show a significant survival advantage. In that study [31], they presented a matched comparison of CBD and CTD at the National Amyloidosis Centre in London, with 3.7 and 3.8 cycles received, respectively. However, 13 patients in the CTD cohort switched to a bortezomib-based regimen after cycle 3, and the follow-up time in the CTD group was twice as long as that of CBD. Although there was no significant difference in OS, patients who received CBD had a superior progression-free survival over those who received CTD (28 mo vs 14 mo). Briefly, the efficacy of bortezomib in patients with AL amyloidosis has not been definitely confirmed and needs to be further explored.

Details of AEs were either absent or inconsistently reported among the included studies, making it difficult to evaluate the toxicities systematically. However, data from the 3 studies [16,17,32] that compared BMD with standard MD showed that the addition of bortezomib might be associated with severe toxicities, even if this was statistically not significant. It is reported that peripheral neuropathy is a major dose-limiting factor of bortezomib [49]. The pooled incidences of all-grade and high-grade peripheral neuropathy of bortezomib in the AL amyloidosis setting were 32.7% and 5.6%, respectively, which are in accordance with the 33.9% and 8.1% in the MM and lymphoma setting [50].

QW seemed to be better than BIW in clinical benefit. One phase 1/2 study [21] (CAN2007) reported that the hematological response rate was comparable between QW and BIW, but QW single-agent bortezomib was better tolerated than BIW in terms of toxicities. The results of our included studies revealed that there was considerable discretion about frequency, and BIW was still the most widely used administration in most areas. We pooled the studies that reported the comparison of QW and BIW as best we could. The pooled proportions of ORR and CHR were similar between the two groups. However, the pooled HR for survival obtained from 3 studies significantly favoured the QW group. We imagine that the higher rate of toxicities in the BIW group and the inconsistency of pooled studies in each analysis may have led to these contradictory results. It is regrettable that we could not obtain a comparison of toxicities between the QW and BIW groups. Therefore, there was no powerful evidence to prove one was more toxic than the other.

Subcutaneous bortezomib has not been systematically studied in patients with AL amyloidosis. One randomized phase 3 study found that subcutaneous bortezomib was not inferior to the standard intravenous administration with respect to treatment efficacy but showed an improved safety profile in the treatment of relapsed MM [51], and the subcutaneous formulation was approved in 2012. However, there were only a few centres using bortezomib by subcutaneous injection to treat patients with AL amyloidosis, and it is impossible to compare different routes of bortezomib according to our included studies.

There were several limitations that cannot be ignored in this systematic review. First, the quality of the included studies was low. There

were only 2 RCTs and 2 prospective phase 1/2 studies among the 24 studies. Among the 6 retrospective studies with controls, two matched comparisons reduced the uncertainty of the results to some extent but could not overcome the retrospective nature. After searching ClinicalTrials.gov, there were no ongoing studies comparing bortezomib with other regimens under the AL amyloidosis setting, and it is hard to run more good-quality trials within a short period. Therefore, there is an urgent need to conduct more high-quality studies. Second, due to the low probability of publishing negative results, publication bias could not be completely avoided. However, the funnel plot seemed symmetrically distributed, and Begg's test revealed that there was no significant publication bias among the 24 studies, nor among the 8 studies with active controls. Third, there was a paucity of data on AEs, with only 8 studies [17,21,24,27,35,37,43,45] reporting relatively detailed toxicities. On the other hand, different studies reported toxicities in different forms (e.g., different grades, different terminology). It was hard to pool every AE in the bortezomib group, let alone compare them with the AEs of other treatments. Maybe we could overcome this limitation by conducting prospective trials. Fourth, the unavoidable variation in the dose/frequency/route/cycles of bortezomib, the use of combined drugs, the severity of the selected patients, and the evaluation criteria introduced great heterogeneity into the pooled results. This suggests that we need to unify the treatment protocols in future clinical trials. Finally, there was a short follow-up time, but long follow-up is essential for assessing survival outcome in original studies. All of these limitations need to be countered in future studies.

In conclusion, our analyses revealed that bortezomib-based regimens offered reasonable ORR, CHR, and organ response in patients with AL amyloidosis. They also showed advantages in ORR, CHR, and cardiac response over none bortezomib regimens. The survival benefit of bortezomib in treating AL amyloidosis patients needs to be verified in more good-quality studies. Moreover, the clinician needs to explore the standardized protocol of using bortezomib in patients with AL amyloidosis. Our meta-analysis indicates that bortezomib-based regimens might be effective therapies for AL amyloidosis patients who are not eligible for or refuse ASCT, with acceptable toxicities. Further well-designed RCTs are needed to provide high-quality evidence.

Funding

This work was supported by the National Natural Science Foundation of China grants 81700584 (M.B.) and 81600562 (Y.W.)

Authorship

Contribution: S.S., B.L., and M.B. designed the study; B.L., M.B., and Y.W. wrote the manuscript; Y.W. and D.W., collected, analysed, and interpreted data; J.Z., R.D., and L.L. collected and analysed data; S.S. and M.B. critically revised the manuscript.

Declarations of Competing Interest

None.

Acknowledgements

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejim.2019.08.011.

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