Ann Hematol (2013) 92:935–943
DOI 10.1007/s00277-013-1711-7

ORIGINAL ARTICLE

Bortezomib for patients with previously untreated multiple myeloma: a systematic review and meta-analysis of randomized controlled trials

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Received: 11 October 2012 / Accepted: 15 February 2013 / Published online: 2 March 2013

Abstract Multiple myeloma (MM) is an incurable disease with a poor survival, which has not been affected even by high-dose chemotherapy. This systematic review was performed to assess the efficacy and safety of the novel agent bortezomib for patients with previously untreated MM. We systematically searched biomedical literature databases and identified randomized controlled trials (RCTs) comparing bortezomib with placebo, no bortezomib, or other active agents for patients with previously untreated MM. Overall survival (OS), reported as hazard ratio (HR) with 95 % confidence interval (CI), was the primary outcome measure. The secondary outcomes included time to progression (TTP), progression-free survival (PFS), and response rates. Five RCTs involving 2,728 patients were included. Three trials compared bortezomib with no bortezomib, and two compared bortezomib with other active agents (vincristine ± adriamycin-based chemotherapy). All included RCTs had methodological shortcomings, including no or unclear allocation concealment and blinding. Compared with no bortezomib or vincristine-based chemotherapy, the bortezomib-based regimen significantly improved the OS of patients with previously untreated MM. HR was 0.71 (95 % CI 0.55–0.93) and 0.77 (95 % CI 0.60–0.99), respectively. However, when compared with the vincristine + adriamycin-based regimen, the OS was similar (HR=0.87, 95 % CI 0.57–1.33). TTP, PFS, and response rates were also improved in patients receiving bortezomib-based regimen. However, the risk of peripheral neuropathy was found to be significantly higher. In summary, bortezomib appears to improve survival and response rates of patients with previously untreated MM in spite of higher risk of peripheral neuropathy.

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Keywords Bortezomib · Multiple myeloma · Systematic review · Meta-analysis

Introduction

Multiple myeloma (MM) is a plasma-cell neoplasm that is characterized by skeletal destruction, renal failure, anemia, and hypercalcemia. MM represented 14 % of new hematological malignancies in the USA in 2003 and almost 19 % of anticipated deaths [1]. MM is an incurable disease with median patients' survival of 5 years. Although sensitive to a variety of chemotherapeutic agents, the response is hardly durable and disease progresses inevitably. With the introduction of novel agents targeting specific pathways involved in the disease process, the overall survival has greatly improved. One of these agents is bortezomib, which was approved by FDA for treatment of MM in 2003 [2].

After the initial diagnosis of MM, patients generally received induction therapy with alkylating agent regimens (such as melphalan plus prednisone) or non-alkylating agent regimens (such as dexamethasone alone or in combination with vincristine and anthracycline) [3]. Alkylating agents are generally confined to the patients ineligible for stem cell transplantation (SCT) since they are myelotoxic and likely to compromise the stem cell reserve [4].

Bortezomib was the first proteasome inhibitor to reach clinical trials for MM. In vitro and in vivo experimental studies have demonstrated that bortezomib alone or combined with a number of conventional cytotoxic agents may induce myeloma cell apoptosis and greatly decrease the myeloma burden [5–9]. For previously untreated MM, some studies have suggested a trend toward improved overall survival for the patients treated with bortezomib [10–12], but the benefit was not definitive. Furthermore, efforts to achieve a significant therapeutic response should be balanced against the need

to avoid significant treatment-related adverse events. Here, we conducted a systematic review and meta-analysis of clinical trials to investigate the efficacy and safety of bortezomib for patients with previously untreated MM.

Methods

Data sources and searches strategy

The following electronic databases were searched: the Cochrane Library (issue 9 of 12, September 2012), MEDLINE/PubMed (1966 to September 2012), EMBASE/Ovid (1980 to September 2012), and the China Biological Medicine Databases (CBM-web, 1981 to September 2012). For the first search, we used terms including the medical subject headings "multiple myeloma" or "plasmacytoma," text words "myeloma" "myelom*," "Plasmacytoma," "Plasmacytom*," "Plasmocytoma," or "Plasmocytom*." For the second search, terms included "velcade," "PS 341," "PS341," "PS-341," "proteasome inhibitor," or "bortezomib." The results from both searches were combined using Boolean operator "AND." A filter for identifying the randomized controlled trials recommended by The Cochrane Collaboration [13] was used to filter out nonrandomized studies in MEDLINE and EMBASE. The conference proceedings were identified by searching the Conference Proceedings Citation Index—Science. Ongoing trials were identified through searching the databases of clinical trial registries (http://clinicaltrials.gov and http://clinicaltrials.nci.nih.gov) in November 2012. Reference lists of all included studies and of reviews related to the topic of the present systematic review were manually searched for other potentially eligible studies. No language and publication status restrictions were applied.

Study selection and data collection

We selected randomized controlled trials (RCTs). The participants were patients with previously untreated myeloma of any stage. The intervention was bortezomib at any dose, for any duration, as monotherapy, or in combination with other agent(s). Acceptable comparisons were bortezomib vs. placebo, bortezomib vs. no bortezomib, and bortezomib vs. other active agent(s). If the participants consisted of patients with previously treated MM and other lymphoproliferative disorders, e.g., lymphoma and Waldenstrom macroglobulinemia, the trials should be excluded unless the subgroup data were available for the patients with previously untreated MM. Potential eligible studies were selected from the search results according to titles and abstracts, and the eligibility of these studies for inclusion was further confirmed after full-text papers were reviewed independently by two review authors (ZZ and JL). Disagreements were resolved by the third author (JC).

Data extraction was performed independently by two reviewers (ZZ and JL). Disagreements were resolved by discussion until consensus was obtained. As much as possible, updated results were sought from the trials' authors, particularly for those published only as meeting abstracts. The data extracted from the trials were entered into the Review Manager (RevMan) software version 5.1 (the Cochrane Collaboration).

Outcome measures

The primary outcome was overall survival (OS), which was defined as time interval from random allocation to death. Alternative definitions, such as time interval from the start of treatment to death, were also included and noted as a potential source of heterogeneity. The secondary outcomes were disease control, such as time to progression (TTP) and progression-free survival (PFS), complete responses (CR), overall responses (OR—partial and complete responses), and adverse events (AEs). TTP was defined as time from randomization to progression. PFS was defined as time from randomization to progression or death. Response with any definition was included.

Assessment of risk of bias in included studies

Two independent authors (ZZ and JL) assessed methodological quality of the included studies. As recommended in the Cochrane Handbook for Systematic Review of Interventions [13], the assessment tool included six specific domains, namely sequence generation, allocation concealment, blinding (patients, personnel, and outcome assessors), incomplete outcome data, selective outcome reporting, and other potential biases. The risk of bias was judged against the following questions: (1) Was the allocation sequence adequately generated? (2) Was the treatment allocation adequately concealed? (3) Was knowledge of the allocated interventions adequately prevented during the study? (4) Were incomplete outcome data adequately addressed? (5) Were reports of the study free of suggestion of selective outcome reporting? (6) Was the study apparently free of other problems that could put it at a risk of bias? In all cases, the answer "yes" indicates a low risk of bias, "no" indicates high risk of bias, and "unclear" indicates either lack of information or uncertainty over the potential for bias [13]. Disagreements were resolved by a third reviewer (JC) until consensus was obtained.

Data synthesis and statistical analysis

We used RevMan 5.1 software for all meta-analyses. First we calculated hazard ratio (HR) and its variance for time-to-

event data (OS and TTP/PFS) whenever the studies did not report, using previously reported methods [14–16]. Then, log(HRs) and their variances of all included trials were pooled together, using inverse variance random-effects model. The results were presented as a HR and 95 % confidence interval (CI). Relative risks (RRs) and 95 % CI for dichotomous data (response rate and AEs) were calculated using the Mantel–Haenszel random-effects model.

Heterogeneity was analyzed by the chi-squared test with significance set at P value 0.10, and the quantity of heterogeneity was measured by I^2 statistic [17]. The origins of heterogeneity, if present, were explored according to differences in methodological quality and characteristics of participants and intervention. Subgroup analyses were conducted on whether patients received SCT. Sensitivity analyses were performed on methodological quality and publication status. Publication bias was assessed unless too few studies were included.

Results

Description of studies

Figure 1 showed the process of selecting and identifying relevant studies in the present systematic review. The search strategy initially yielded 3,242 records. Two hundred ninety-five potentially relevant RCTs were selected according to titles and abstracts. Among them, 41 were evaluated in detail. Eventually, five RCTs [18–22] were included and their characteristics were described in Table 1.

All these five trials were conducted between 2004 and 2009 and published as full text. The sample size ranged from 257 to 827 and the total number of patients was 2,728. In all these trials, bortezomib was used for induction remission. In four trials [19–22], bortezomib induction therapy was followed by autologous stem cell transplantation (ASCT). Three RCTs [18–20] compared bortezomib with nothing (no bortezomib), and two [21, 22] compared bortezomib with other active agents (vincristine ± adriamycin-based chemotherapy). Primary outcomes and secondary outcomes (e.g., PFS and OR) were reported in these trials (Table 1). Individual patient data were not available in spite of our effort to obtain them.

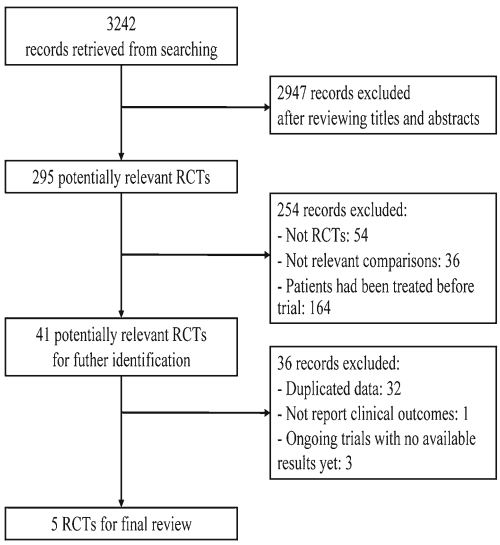

Fig. 1 Flow chart of trials selection and identification. *RCTs* randomized controlled trials

Risk of bias in included studies

The details of the methodological quality of individual trials were summarized in Table 2. All trials claimed randomized assignment, but only one RCT [19] mentioned randomization method (generated by computer) and allocation concealment (allocated by the coordinating center). Therefore, both of the methods of randomization and allocation concealment were judged as "yes" for this trial. Effort has been made to contact the trials' authors for further information. Only one trial [22] author responded and provided the information about the randomization method (generated by computer) and allocation concealment (not used). For blinding, four open-label RCTs [18–22] were judged as "no," and the remaining one RCT [20] was unclear. As all the included trials did not use placebo as control, strict blinding was impossible. These included studies [18–22] explicitly provided the number of and reasons for withdrawal or loss to follow-up, and reported the use of an intention-to-treat analysis. In all included studies, the protocol is available, and all of the study's pre-specified (primary and secondary) outcomes have been reported in the pre-specified way. All trials [18–22] claimed they were not free of interest conflict concerning the manufacturer of bortezomib.

Measures of treatment effect

Bortezomib vs. no bortezomib

Three trials [18–20] compared bortezomib with no bortezomib (Table 1). OS, TTP, PFS, and response rate were reported in these trials. We used previously reported methods [14–16] to estimate their log(HRs) and variance for OS and TTP in two RCTs [18, 19], and for PFS in one RCT [19]. We were unable to estimate log(HRs) and variance for OS and PFS in the Rosinol study [20] because of lack of data. We have tried to contact the authors but failed so far.

Primary outcome

Overall survival

Among the three trials reporting OS, only one RCT [18] showed bortezomib significantly improved OS. In the

Table 1 Characteristics of included studies

Studies	No. of patients	Induction regimens Drugs (day administered)×no. of cycles (duration, days)		ASCT was planned?	Outcomes	Publication status
		Expt	Ctrl			
Mateos et al. [18]	682	BOZ 1.3mg/m^2 (1, 4, 8, 11, 22, 25, 29, 32)×4 (42) then (1, 8, 22, 29)×5 (42) MEL 9mg/m^2 (1, 4)×9 (42) PRE 60mg/m^2 (1, 4)×9 (42)	MEL 9mg/m^2 (1, 4)×9 (42) PRE 60mg/m^2 (1, 4)×9 (42)	No	OS, TTP, CR, PR, AEs	Full text
Cavo et al. [19]	480	BOZ 1.3mg/m^2 (1, 4, 8, 11)×3 (21) DEX 40mg/day (1, 2, 4, 5, 8, 9, 11, 12)×3 (21) THL 200mg/day (1–21)×3 (21)	DEX 40mg/day (1, 2, 4, 5, 8, 9, 11, 12)×3 (21) THL 200mg/day (1–21)×3 (21)	Yes	OS, TTP, PFS, CR, PR, AEs	Full text
Rosinol et al. [20]	257	Exp 1: BOZ 1.3mg/m^2 (1, 4, 8, 11)×6 (28) THL 200mg/day×6 (28) DEX 40mg/day (1–4, 9–12)×6 (28) Exp 2: BOZ (1.3mg/m^2 on days1, 4, 8, 11)×2 (21) an alternating basis of VBMCP/VBAD×4cycles;	THL 200mg/day×6 (28) DEX 40mg/day (1–4, 9–12)×6 (28)	Yes	OS, PFS, CR, AEs	Full text
Harousseau et al. [21]	482	BOZ 1.3mg/m^2 (1, 4, 8, 11)×4(21) DEX 40mg/day [1–4 (cycles 1–4), 9–12 (cycles 1, 2)]±DECP×4 (21)	VIN+ADRIA+DEX±DECP×4(21)	Yes	OS, PFS, CR, PR, AEs	Full text
Sonneveld et al. [22]	827	BOZ 1.3mg/m^2 (1, 4, 8, 11)×3 (21) ADRIA 9mg/m^2 (1, 4)×3 (21) DEX 40mg/day (1–4, 9–12, 17–20)×3 (21)	VIN 0.4mg×3 (21) ADRIA 9mg/m^2 (1, 4)×3 (21) DEX 40mg/day (1–4, 9–12, 17–20)×3 (21)	Yes	OS, PFS, CR, PR, AEs	Full text

Abbreviations: *Expt* experimental arm; *Ctrl* control arm; *BOZ* bortezomib; *MEL* melphalan; *PRE* prednisone; *DEX* dexamethasone; *THL* thalidomide; *ADRIA* adriamycin; *VIN* vincristine; *VBMCP* regimen including vincristine, BCNU, melphalan, cyclophosphamide, and prednisone; *VBAD regimen including vincristine, BCNU, adriamycin, and dexamethasone; ASCT autologous stem cell transplantation; OS overall survival; TTP time to disease progression; PFS progression-free survival; CR complete response; PR partial response; AEs adverse events*

Table 2 Risk of bias in included studies

Studies	Adequate sequence generation?	Adequate allocation concealment?	Blinding?	Addressed incomplete outcome data?	Free of selective outcome reporting?	Free of other bias?
Mateos et al. [18]	Unclear	Unclear	No[e]	Yes[f]	Yes[g]	No[h]
Cavo et al. [19]	Yes[a]	Yes[c]	No[e]	Yes[f]	Yes[g]	No[h]
Rosinol et al. [20]	Unclear	Unclear	Unclear	Yes[f]	Yes[g]	No[h]
Harousseau et al. [21]	Unclear	Unclear	No[e]	Yes[f]	Yes[g]	No[h]
Sonneveld et al. [22]	Yes[a, b]	No[b, d]	No[e]	Yes[f]	Yes[g]	No[h]

In all cases, the answer "yes" indicates a low risk of bias, "no" indicates high risk of bias, and "unclear" indicates either lack of information or uncertainty over the potential for bias

[a] Random sequences generated by computer

[b] Information obtained from primary authors

[c] Allocated by the coordinating center

[d] Not used allocation concealment

[e] Open-label RCT

[f] Provided the number of and reasons for withdrawal or loss to follow-up and used intention-to-treat analysis

[g] Reported the study's pre-specified outcomes

[h] Supported by the manufacturer of bortezomib

other two trials, the Cavo study [19] and the Rosinol study [20], there was no significant difference in OS between the bortezomib group and no bortezomib group. Calculation of log(HR) and variance for OS was possible in the Mateos study [18] and the Cavo study [19]. HR for OS was 0.65 (95 % CI 0.51–0.84) and 0.88 (95 % CI 0.55–1.41), respectively (Fig. 2). The pooled HR for OS showed there was 29 % reduction in risk of death when bortezomib was added to induction therapy (HR 0.71, 95 % CI 0.55–0.93) with no significant heterogeneity across these two studies (P=0.26 and I^2=20 %).

Secondary outcome

Time to progression and progression-free survival

Two trials [18, 19] reported TTP and both showed TTP was significantly longer in the bortezomib-based therapy. HR for TTP was 0.48 (95 % CI 0.37–0.62) and 0.61 (95 % CI 0.43–0.87) in the Mateos study [18] and the Cavo study [19], respectively (Fig. 2). From these two trials, the pooled HR also showed that the risk of disease progression was significantly lower in the bortezomib group (HR 0.52, 95 % CI 0.42–0.66). There was no significant heterogeneity across these two studies (P=0.28 and I^2=16 %).

Two trials [19, 20] reported PFS, and both claimed bortezomib significantly improved PFS. In the Cavo study [19], the estimated 3-year rate of PFS was 68 % in the bortezomib group and 56 % in the no bortezomib group, respectively. HR for PFS was 0.63 (95 % CI 0.45–0.88; Fig. 2). Detailed PFS data was not available in Rosinol study [20].

Complete responses and overall responses

All three trials [18–20] reported complete responses and overall responses. Pooled results showed that the bortezomib-treated group achieved a statistically significant higher rate of CR compared with the no bortezomib group (RR, 4.31; 95 % CI 2.05–9.05; P=0.0001; Fig. 3a). The absolute risk increase for CR was 21.0 % (95 % CI 17.3–24.7 %). The number needed to treat in order to achieve one additional CR was 5 (95 % CI 4–6) when a bortezomib-containing therapy was applied. For OR, there was also significant difference between the bortezomib group and no bortezomib group (RR, 1.48; 95 % CI 1.02–2.14; P=0.04; Fig. 3b).

There was a high degree of statistical heterogeneity among the reported CR and OR as indicated by the chi-squared test for heterogeneity (P=0.006 and P<0.0001, respectively) and by I^2 values (81 and 96 %, respectively).

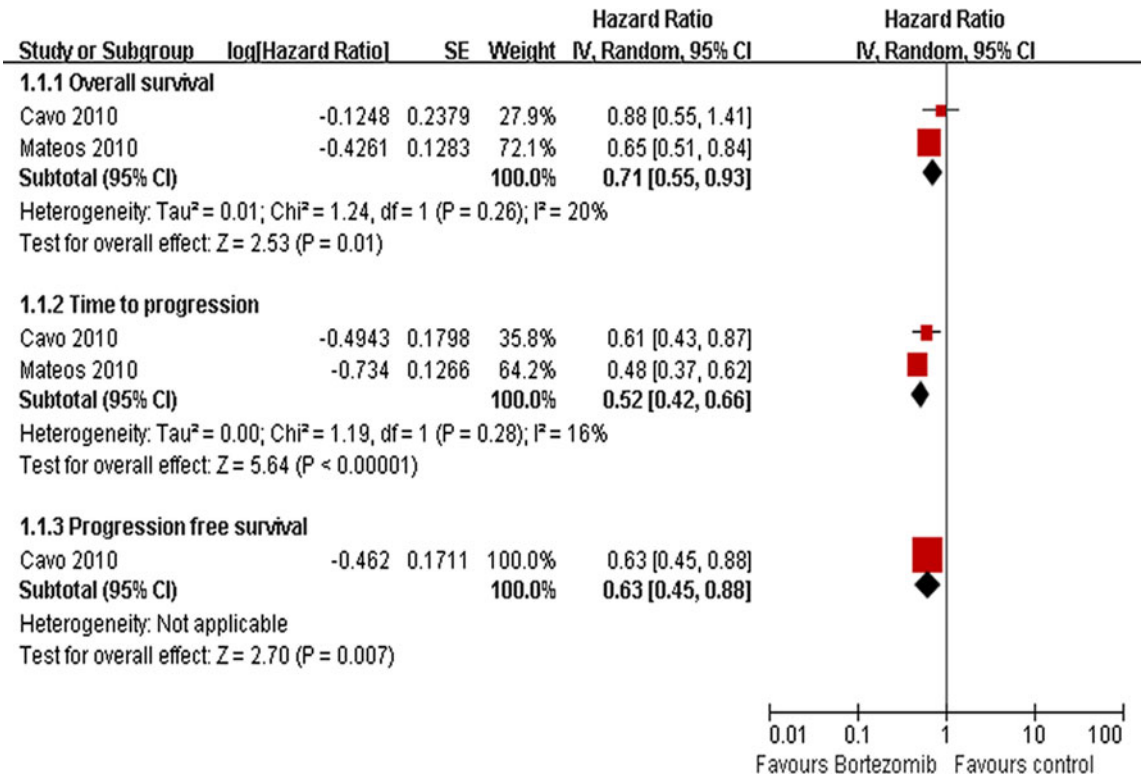

Fig. 2 Meta-analysis of overall survival and disease control in the trials comparing bortezomib with no bortezomib. *SE* standard error, *IV* inverse variance, *CI* confidence interval

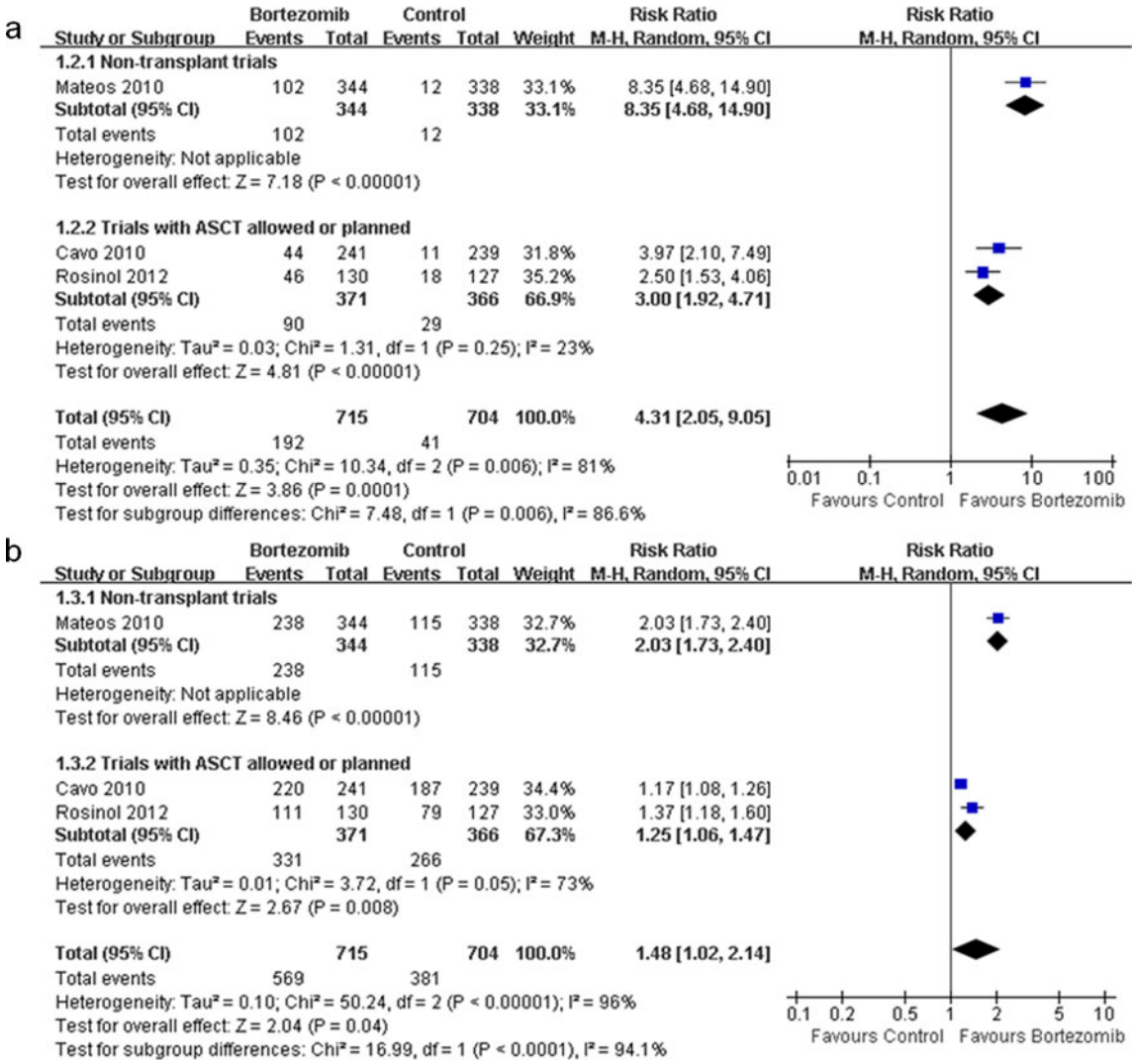

Fig. 3 Meta-analysis of response rates in the trials comparing bortezomib with no bortezomib. **a** Complete responses, **b** overall responses. *M-H* Mantel–Haenszel, *CI* confidence interval

This heterogeneity was possibly because the patients received ASCT in two trials [19, 20] but did not in the other one [18]. When trial(s) with and without ASCT were analyzed separately, there is no significant heterogeneity (Fig. 3). Subgroup analyses also revealed that the bortezomib arm had statistically significant higher CR and OR than the no bortezomib arm whether or not the patients received ASCT.

Adverse events

All three trials [18–20] provided data of AEs, including treatment-related mortality (TRM), peripheral neuropathy (PNP), thrombotic events, herpes zoster, thrombocytopenia, skin rash, nausea, etc. It was not possible to perform a summary statistic of all AEs because their definitions were different across trials. The most frequently reported AEs among patients receiving induction bortezomib were TRM, grade 3/4 PNP, and grade 3/4 thrombotic events.

TRM data were available in all three studies [18–20]. The pooled results showed there was no significant difference in TRM between the bortezomib group and the no bortezomib group (RR=0.58, 95 % CI 0.23–1.49; P=0.26; Fig. 4) with no heterogeneity across studies (P=0.72 and I^2=0 %). For PNP (grade 3/4), these three studies [18–20] showed that bortezomib increased risk of PNP. RR was 87.45 (95 % CI 5.41–1,414.13), 4.56 (95 % CI 1.76–11.80), and 2.77 (95 % CI 1.13–6.79), respectively, in the Mateos study [18], the Cavo study [19], and the Rosinol study [20]. The pooled RR was 6.37 (95 % CI 1.41–28.75). The heterogeneity between these three studies was prominent (P=0.02 and I^2=76 %). For thrombotic events (grade 3/4), the pooled RR was 2.20 (95 % CI 0.97–4.96) with no significant heterogeneity (P=0.62 and I^2=0 %) across these three studies [18–20].

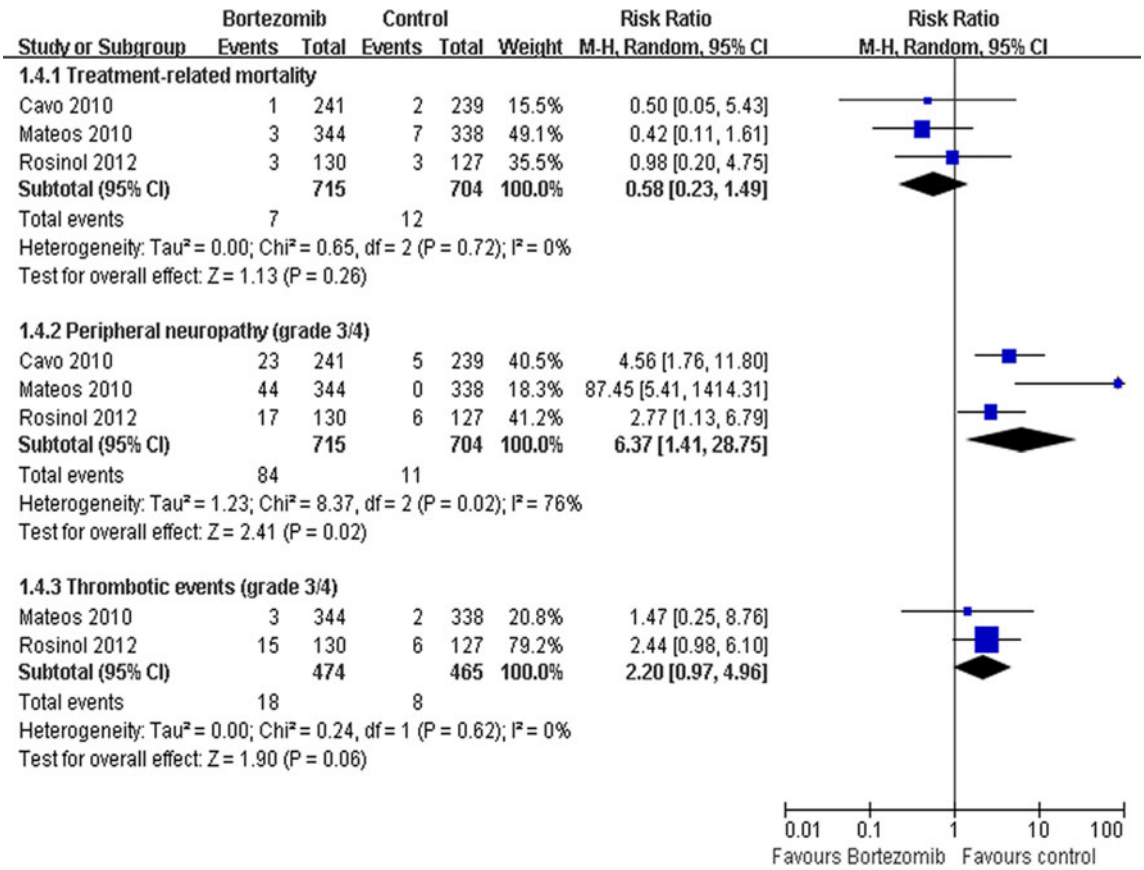

Fig. 4 Meta-analysis of adverse events in the bortezomib group compared to the no bortezomib group (treatment-related mortality, grade 3/4 peripheral neuropathy, and grade 3/4 thrombotic events). *M-H* Mantel–Haenszel, *CI* confidence interval

Bortezomib vs. other active agents

Bortezomib + dexamethasone vs. vincristine + adriamycin + dexamethasone One trial [21] compared bortezomib + dexamethasone (PD) with vincristine + adriamycin + dexamethasone (VAD; Table 1). The outcome measures were OS, PFS, CR, OR, and AEs. No statistically significant difference was found in OS and PFS. The study [21] reported similar OS between the PD group and the VAD group after median follow-up of 32.2 months. The 3-year OS rates were 83.3 and 81.4 %, respectively (P=0.5079). Median PFS was 36.0 vs. 29.7 months (P=0.064). The calculated HRs for OS and PFS was 0.87 (95 % CI 0.57–1.33) and 0.79 (95 % CI 0.61–1.01), respectively. However, the patients treated with PD regimen were significantly more likely to achieve CR (RR 4.37, 95 % CI 1.26–15.14) and OR (RR 1.29, 95 % CI 1.13–1.47) than those treated with VAD regimen.

AEs including TRM, PNP (grade 3/4), and thrombotic events (grade 3/4) were reported in this study. There was no significant difference in TRM between the PD group and the VAD group (RR, 0.07; 95 % CI 0.00–1.17). PNP was more likely to occur in the PD group compared with the VAD group (RR, 3.43; 95 % CI 1.29–9.14), but thrombotic events (grade 3/4) were lower in the PD group (RR=0.31, 95 % CI 0.10–0.94).

Bortezomib + adriamycin + dexamethasone vs. vincristine + adriamycin + dexamethasone Only one trial [22] compared bortezomib + adriamycin + dexamethasone (PAD) with VAD (Table 1). The outcome measures were OS, PFS, CR, OR, and AEs. The study reported that both OS and PFS were superior in the PAD arm compared with the VAD arm. The calculated HRs for OS and PFS was 0.77 (95 % CI 0.60–0.99) and 0.74 (95 % CI 0.62–0.89), respectively. The patients treated with PAD regimen were also significantly more likely to achieve CR (RR, 4.15; 95 % CI 1.84–9.37) and OR (RR, 1.45; 95 % CI 1.31–1.61) than those treated with VAD regimen.

For AEs, TRM, PNP (grade 3/4), and thrombotic events (grade 3/4) were reported. TRM and thrombotic events (grade 3/4) were not significantly different between the PAD group and VAD group. RR was 1.30 (95 % CI 0.48–3.51) and 1.34 (95 % CI 0.30–6.02), respectively. PNP was also more likely to occur in the PAD group compared with the VAD group (RR, 2.49; 95 % CI 1.18–5.28).

We did not perform sensitivity analysis and publication bias assessment because only a few trials were included in the present systematic review and meta-analysis.

Discussion

To evaluate the efficacy and safety of bortezomib for patients with previously untreated myeloma, we conducted a systematic search and identified five RCTs [18–22]. These trials provided the information on the efficacy of bortezomib for induction treatment.

Three trials [18–20] compared bortezomib with no bortezomib. For OS, only two RCTs [18, 19] provided data for the present review. TTP was reported in two RCTs [18, 19], and PFS data were available in only one trial [19]. Analyses of these data showed that bortezomib conferred a significant survival advantage among patients with previously untreated myeloma (Fig. 2). CR and OR were reported in all these three trials [18–20]. The bortezomib group had higher CR and OR than the no bortezomib group, either in the individual study or in pooled results, indicating the obvious benefit of bortezomib for improvement of survival and response in previously untreated myeloma. We have noted that statistical heterogeneity existed in our meta-analysis of response rates. A major source of heterogeneity, we thought, was different participants in these trials. As shown in Fig. 3, effect of bortezomib on responses of nontransplantation settings is stronger than that of transplantation settings. Although we used pre-ASCT response rates, the patient populations and treatment protocols are quite different in ASCT vs. non-ASCT trials. It is likely that participants in non-ASCT trials received more cycles of bortezomib contributed to the differences in response rates. Patients in non-ASCT trials are older, but this might not be the reason that they got more benefit from bortezomib.

For the toxicities of bortezomib, all these three studies [18–20] reported that TRM data and our meta-analysis showed bortezomib did not increase the risk of treatment-related death. We noted that TRM is consistently favorable for bortezomib in Fig. 4. This likely reflected that bortezomib-containing regimens may be well tolerated and more capable of controlling disease progress and related complications. But this was not the case for PNP (grade 3/4) and thrombotic events (grade 3/4) in Fig. 4. Our meta-analysis showed bortezomib increased the risk of thrombotic events although the difference did not arrive at the level of statistical significance. However, the addition of bortezomib to MP (melphalan plus prednisone) or TD (thalidomide plus dexamethasone) induction therapy did significantly increase the risk of PNP (RR, 6.37; 95 % CI 1.41–28.75). Therefore, there should be careful trade-off between benefit and harm and adequate informed consent when deciding bortezomib-based induction chemotherapy.

Two trials [21, 22] compared bortezomib with other active agents. The Harousseau study [21] compared PD with VAD and showed the advantageous effect of bortezomib on response rate but no benefit on survival and PFS. Besides, bortezomib significantly increases risk of PNP. Another study [22] compared PAD with VAD regimen, showing that PAD regimen conferred significant benefit on both survival and response rates. Again, PNP was more common in the PAD group (RR, 2.49; 95 % CI 1.18–5.28).

Several limitations should be considered when interpreting the result of the present review. First, there were methodological problems in all the included trials. Most trials did not take measures of blinding. The allocation concealment was not used or unclear, except for the Cavo study [19]. Therefore, potential bias, such as assessment bias, participant selection bias, etc., was likely to exist. Second, all our analyses were based on published summary results instead of individual patient data which were considered to be more reliable [23]. Third, our review is vulnerable to publication bias. Despite an exhaustive and thorough search, it is possible that negative trial results of bortezomib may not have been published. Fourth, our analyses were limited to the data available in the publications.

This is the first systematic review and meta-analysis of RCTs evaluating bortezomib for previously untreated myeloma. Comparing to the no bortezomib group, the results suggested that the addition of bortezomib to induction therapy for these patients offered marked clinical benefits in terms of OS, TTP, PFS, and response, but did not increase treatment-related mortality. Bortezomib's benefit on response rate was significant in both the study comparing PD with VAD and the study comparing PAD with VAD. Therefore, bortezomib-based therapy should be considered as the promising induction regimen for patients with previously untreated myeloma. However, potential risk of PNP should be taken into account.

Acknowledgments This work was supported by the National Natural Science Foundation of China (no. 30871111 and 81172259) and the Natural Science Foundation of Fujian Province of China (no. 2011J05064). We would like to thank Dr. Sonneveld for providing additional information about their trial.

Conflict of interest The authors declare that they have no conflict of interest.

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