Int J Clin Exp Med 2017;10(1):293-306
www.ijcem.com /ISSN:1940-5901/IJCEM0019140

Original Article

Evaluation of bortezomib and dexamethasone-based treatment in patients with multiple myeloma: a meta-analysis

Lihong Shou, Dan Cao, Xiaohui Dong

Department of Hematology, Huzhou Central Hospital, Huzhou 313000, Zhejiang, China

Received November 4, 2015; Accepted February 10, 2016; Epub January 15, 2017; Published January 30, 2017

Abstract: Multiple myeloma (MM) is the second most frequent hematologic malignancy, and the evaluations of standard therapeutic effects were inconsistent. The study was aimed to provide a comprehensive assessment of bortezomib-cyclophosphamide-dexamethasone (VCD), bortezomib-thalidomide-dexamethasone (VTD) and VTDC (VTD plus cyclophosphamide) regimens for the MM management. Electronic databases such as PubMed, EMBASE and Cochrane were retrieved from their inception to April, 2015. Eligible studies were selected with predefined criteria. Four main outcomes as ORR (overall response rate), CR (complete response), VGPR (very good partial response) and PR (partial response); and the adverse effects were evaluated, basing on the Cochran Q and I^2 test. The independent-samples T test was used. Statistical analysis was performed using STATA and SPSS. A set of 11 studies were identified for the meta-analysis. All the regimens achieved a higher response on the newly diagnosed MM than the relapsed MM. VCD and VTD had a comparable efficiency on the ORR, VGPR and PR. However, VTD had a pronounced higher CR than VCD on the newly diagnosed MM patients ($P < 0.05$). VTDC achieved an increase CR (0.46 vs. 0.082 or 0.326) but a decreased risk of thrombocytopenia (0.06 vs. 0.11 or 0.083) than either VCD or VTD for the newly diagnosed MM. Besides, no difference between VCD and VTD was observed in terms of the toxicity tolerance ($P < 0.05$). For newly diagnosed MM patients, VTD was comparable with VCD in terms of ORR, VGPR and PR, but superior to VCD in CR.

Keywords: Bortezomib, cyclophosphamide, dexamethasone, thalidomide, response, toxicity effects, meta-analysis

Introduction

Multiple myeloma (MM) is the second most frequent hematologic malignancy worldwide [1], with the hallmark of clonal proliferation of plasma cells in the bone marrow [2]. Annually, it is estimated that approximately 86,000 cases are diagnosed with MM, and nearly 63,000 individuals are reported to die from this disease [3]. The increased risks of infection, pancytopenia, as well as bone diseases are the remarkable clinical features of MM [4]. Despite the fact that the disease is deemed as incurable, several improvements of the outcomes have been achieved owing to the advanced therapeutic approaches, such as high-dose chemotherapy with hematopoietic stem cell transplantation (HSCT) and the novel agents [5, 6]. The response is increased and the survival is prolonged; however the relapse is still inevitable [7].

As a potent proteasome inhibitor, bortezomib is considered having the anticancer activity. The single agent has been used as a frontline therapy for MM management [8]. It is well known that vincristine, doxorubicin and dexamethasone (VAD) has been used as the pre-inducing therapy for patient who would undergo the stem-cell transplantation [9]; however, its application on MM patients is limited due to the high dose need of dexamethasone [10]. Recently, the administration of thalidomide, in combination of corticosteroids and alkylating has been introduced in the management of the relapsed MM [11]. Additionally, the combination of thalidomide with dexamethasone has been demonstrated advantageous than the use of dexamethasone alone for the newly diagnosed MM [12]. Cyclophosphamide acts as a second and less stem cell toxic alkylator in the treatment of MM due to the well-tolerated outcome [13].

At present, three-drug induction regimens such as bortezomib-cyclophosphamide-dexamethasone (VCD) and bortezomib-thalidomide-dexamethasone (VTD) have been established as the standard for MM treatment. Multiple studies have been conducted to compare the efficiency of the therapies with three-drug combinations to that with two or single agents [14, 15]. It is clarified that VTD is more beneficial than thalidomide-dexamethasone to the newly diagnosed MM patient after autologous HSCT [16]. Coincidently, VCD is also demonstrated to be superior to bortezomib plus dexamethasone for the initial MM treatment [17]. Furthermore, the four-drug combinations such as bortezomib, dexamethasone,cyclophosphamide,andlenalidomide and bortezomib, cyclophosphamide, thalidomide, and dexamethasone (VTDC) are also applied for the treatment of MM [10, 18]. However, assessments of the therapeutic effectiveness among VCD, VTD and VTDC are inconsistent. More recently, a meta-analysis compares the curative effects of VCD and VTD and proposes that VTD therapy might be more advantageous and more tolerant than VCD for the newly diagnosed transplant-eligible MM patients [19]. Nevertheless, the relapsed MM and the VTDC evaluation are not concerned in their study. Besides, the sample size is relatively small because only eight studies containing 672 patients have been included. To better shed light on the exact evaluation, we carried out this meta-analysis, which included 11 studies involving the therapeutic efficiency with regard to VCD or VTD, or VTDC, and compared the differences between VCD and VTD treatments using independent-samples T test. Moreover, subgroup analysis stratified by MM type (newly diagnosed or relapsed MM) was performed, aiming to provide a comprehensive understanding of the optimal strategy for MM treatment.

Materials and methods

Search strategy

The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines for the reporting of systematic reviews and meta-analysis were applied to carry out this meta-analysis [20]. Literatures were retrieved in the databases including PubMed, EMBASE and Cochrane from their inception to April, 2015. The key words were “bortezomib” AND “dexamethasone” OR “cyclophosphamide” OR “thalidomide” AND “multiple myeloma” OR “MM”.

Two researchers independently conducted the retrieval through title browsing, abstract reading or full text reading. The disagreements were resolved by the discussion with a third investigator.

Inclusion and exclusion criteria

Studies were included if the following criteria were fulfilled: (1) they were prospective studies; (2) participants were patients with MM; (3) therapeutic effects of the agents such as bortezomib, dexamethasone, cyclophosphamide or thalidomide were evaluated; (4) at least one of the outcomes including overall response rate (ORR), complete response (CR), very good partial response (VGPR), partial response (PR) and the adverse effects in grade 3-4 were involved in the study; (5) if multiple publications were based on the same dataset, only the study containing the comprehensive outcomes was included for the meta-analysis. On the other hand, the exclusion criteria for the studies were: (1) the study was a retrospective study; (2) the study lacked the data information of VCD, VTD or VTDC; (3) the study was a reviewer, meeting report or letter; (3) the study was not an English publication.

Data extraction

The data were abstracted by two independent individuals and the disagreements were resolved through the discussion with a third investigator. The following information was extracted such as the first author, publication time, research region, research time, follow up time, the populations, case numbers, mean age, administration strategy, the specific values of ORR, CR, VGPR and PR, and the adverse effect assessments.

Statistical analysis

The main outcomes for the meta-analysis were ORR, CR, VGPR and PR. The adverse effect indicators such as thrombocytopenia, leukocytopenia, neutropenia, fatigue, neuropathy and diarrhea were estimated basing on physical examination, records of vital signs, toxicity assess-

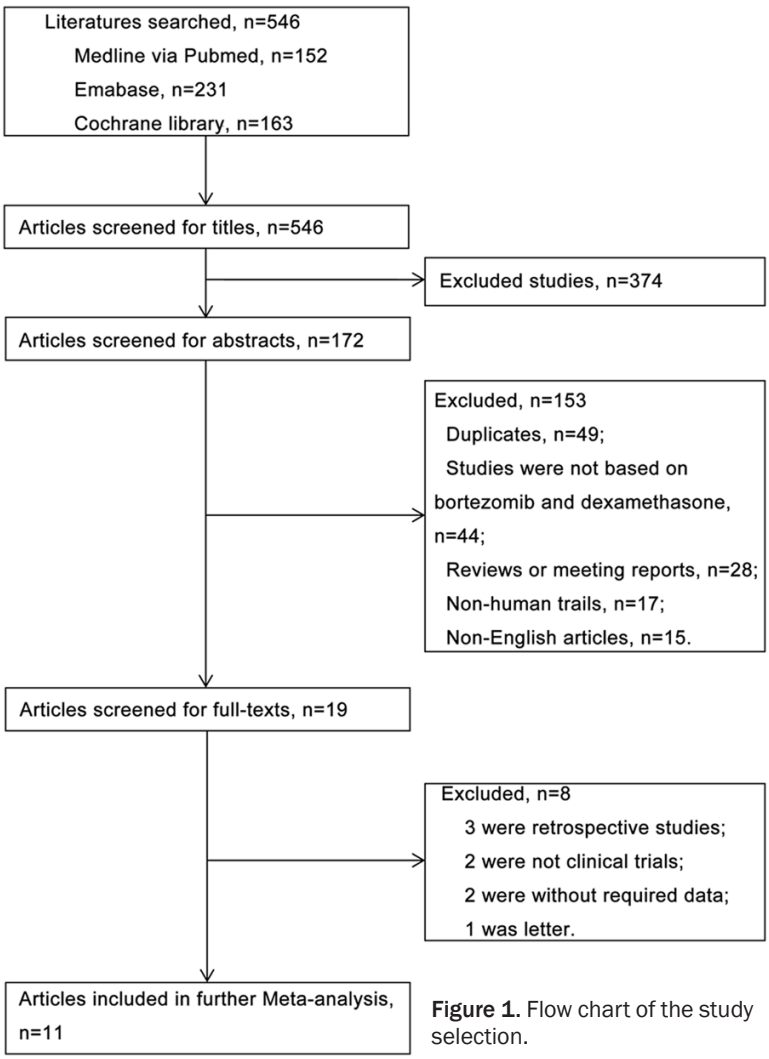

Figure 1. Flow chart of the study selection.

ware [24], and $P < 0.05$ indicating the significance. Additionally, subgroup analysis stratified by the categories of MM (newly diagnosed or relapsed MM) was performed.

Results

Studies included in the meta-analysis

A cohort of 546 studies was identified through the preliminary search in the databases (152 in PubMed, 163 in Cochrane library and 231 in Embase). After title browsing, a total of 374 studies were eliminated. Then another removal of irrelevant studies was carried out (including 49 duplicated publications, 28 letters, 44 studies not involving bortezomib and dexamethasone, 17 non-human clinical research and 15 non-English publications). Afterwards, the remaining 19 studies were subjected to full text reading, by which 8 studies were excluded (3 were retrospective studies, 2 were non-clinical studies and 2 not providing sufficient data information). Finally, a set of 11 studies [10, 13, 14, 17, 25-31] were included in this meta-analysis. The detailed selection procedure is presented as **Figure 1**.

Characteristics of the selected studies

Among the 11 identified studies, 7 studies involved the therapeutic effect evaluation of VCD [13, 14, 25-29], one study evaluated the VTD treatment [30] and one assessed the VTDC [10]. He and colleagues reported both the VCD and VTD administrations [17], while Ludwig's study included the evaluation of both VTD and VTDC [31]. As shown in **Table 1**, the identified studies were distributed in Asia, Europe and America, and the MM patients of the included studies were newly diagnosed or relapsed, or previously untreated with the

ment and laboratory test; and were classified referring to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCICTCAE version 3.0, http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf). The heterogeneity across the selected studies was determined by Cochran Q and I^2 test [21], using the software of STATA (version 11.0, STATA, College Station, TX, USA) [23]. Substantial heterogeneity was indicated if $P < 0.05$ or $I^2 > 50\%$, when a random-effects model should be selected; otherwise, if homogeneity was suggested ($P > 0.05$ or $I^2 < 50\%$), a fix effect model was applied. Then each outcome index was pooled in a selected model. The outcome differences between VCD and VTD groups were detected by independent-samples T test [22] using SPSS (version 19.0, SPSS. Inc., Chicago, Illinois) soft-

Table 1. Characteristics of the included studies

Author, year	Country	Study period	Follow-up, months	Population	Group	Age, year	No. (M/F)
Bensinger, 2010	USA	2006.05-2008.06	20.9	Newly diagnosed and symptomatic MM	VCD	58 (38-83)	44 (30/14)
Fu, 2012	China	2004.09-2007.04	NR	Relapsing MM	VCD	61 (37-78)	44 (33/11)
Kropff, 2007	Germany	2004.04-2005.01	NR	Relapsed MM	VCD	NR	54 (35/19)
Kropff, 2009	Germany	2006.03-2007.02	NR	Newly diagnosed MM	VCD	50.8 (36-60)	31 (16/15)
Kumar, 2012	USA	2008.06-2009.09	22	Previously untreated symptomatic MM	VCD	62 (40-75)	33 (19/14)
Mai, 2015	Germany	2010.07-2012.10	NR	Newly diagnosed, transplant-eligible MM	VCD	58.7 (33-70)	251 (153/98)
Reeder, 2009	Canada	NR	NR	Newly diagnosed and symptomatic MM	VCD	60 (38-75)	33 (17/16)
Rosinol, 2012	Spain	2006.04-2009.03	24	Newly diagnosed and untreated symptomatic MM	VTD	56	130 (72/58)
Kim, 2010	Korea	2004.11-2008.11	12.6 (1.7-49.6)	Relapsed or refractory MM	VCTD	64 (39-76)	70 (35/35)
He, 2014	China	2006.02-2013.05	22.5 (2-64)	Newly diagnosed symptomatic MM	VCD	60 (31-83)	77 (35/32)
					VTD		34 (24/10)
Ludwig, 2013	Europe	2007.10-2008.09	33.3 (28.2-36.8)	Previously untreated, measurable MM	VTD	57 (35/65)	49 (26/23)
			33.1 (28.2-39.7)		VCTD	58 (33-68)	49 (25/24)

Abbreviations: V: bortezomib; D: dexamethasone; C: cyclophosphamide; T: thalidomide; MM: multiple myeloma; M: male; F: female; NR: not reported.

Table 2. Dose strategy of the included studies

Study	Bortezomib	Dexamethasone	Cyclophosphamide	Thalidomide	Cycles	Outcomes
Bensinger, 2010	1.3 mg/m^2 on days 1, 4, 8, 11	40 mg on day of and day after bortezomib	300 mg/m^2 on days 1, 8		Three 21-day cycles	ORR, CR, VGPR, PR, AE
Fu, 2012	1.3 mg/m^2 IV on days 1, 4, 8, 11	20 mg/m^2 orally daily for 4 days beginning on days 1, 9 and 17	70 mg/m^2 orally twice daily for 4 days			ORR, CR, PR, AE
Kropff, 2007	1.3 mg/m^2 on days 1, 4, 8, and 11, followed by three 5-week cycles with V 1.3 mg/m^2 on days 1, 8, 15, and 22	20 mg/d orally	Continuous oral treatment at a dose of 50 mg/d p.o.		3-week cycles	ORR, CR, PR, AE
Kropff, 2009	1.3 mg/m^2 on days 1, 4, 8, and 11	40 mg on the day of bortezomib injection	900, 1,200, or 1,500 mg/m^2 on day 1		21-day cycles	ORR, CR, PR, AE
Kumar, 2012	1.3 mg/m^2 on days 1, 4, 8, 11	40 mg on days 1, 8, 15	500 mg/m^2 on days 1, 8		3-week cycles	ORR, CR, VGPR, AE
Mai, 2015	1.3 mg/m^2 on days 1, 4, 8, 11	40 mg on days 1-2, 4-5, 8-9, 11-12	900 mg/m^2 i.v. on day 1, and p.o.		320 mg/cycle, repeated every 21 days	ORR, CR, VGPR, PR, AE
Reeder, 2009	1.3 mg/m^2 IV on days 1, 4, 8 and 11	40 mg orally on days 1-4, 9-12 and 17-20	300 mg/m^2 orally on days 1, 8, 15 and 22		28-day cycle for four cycles	ORR, VGPR, PR, AE
Rosinol, 2012	2 cycles 1.3 mg/m^2 on days 1, 4, 8, and 11 at 3-week intervals	40 mg orally on days 1-4 and 9-12 at 4-week intervals		200 mg daily (escalating doses in the first cycle: 50 mg on days 1 to 14, and 100 mg on days 15 to 28)		CR, VGPR, PR, AE
Kim, 2010	1.3 mg/m^2 IV on days 1, 4, 8, and 11	20 mg/m^2 IV on days 1, 4, 8, and 11	150 mg/m^2 orally on days 1-4	50 mg/day orally every day	Two cycles	ORR, CR, VGPR, PR, AE
He, 2014	1.3 mg/m^2 IV on days 1, 4, 8, 11	20 mg/day IV on days 1-2, 4-5, 8-9, 11-12	200 mg/m^2 IV on days 1-4	100 mg orally each day		ORR, VGPR, PR, AE
Ludwig, 2013	1.3 mg/m^2 on days 1, 4, 8, and 11	40 mg on days 1-4 and 9-12	400 mg/m^2 IV per day on days 1 and 8	100 mg on days 1 through 21	Four 21-day cycles	ORR, CR, VGPR, PR, AE

Abbreviations: IV: intravenously; p.o.: by months; ORR: overall response rate; CR: complete response; VGPR: very good partial response; PR: partial response; AE: adverse events.

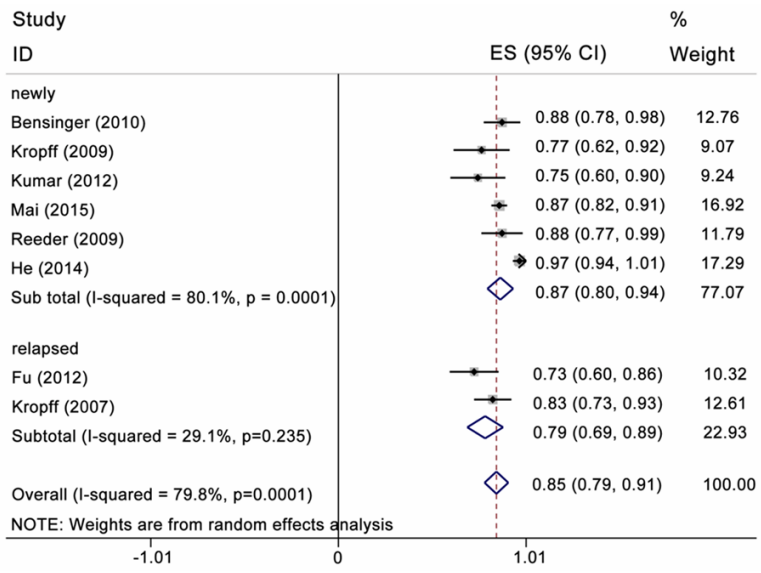

Figure 2. Evaluation of overall response rate with bortezomib-cyclophosphamide-dexamethasone (VCD) regimen for multiple myeloma treatment. ES: effect size; CI: confidence interval.

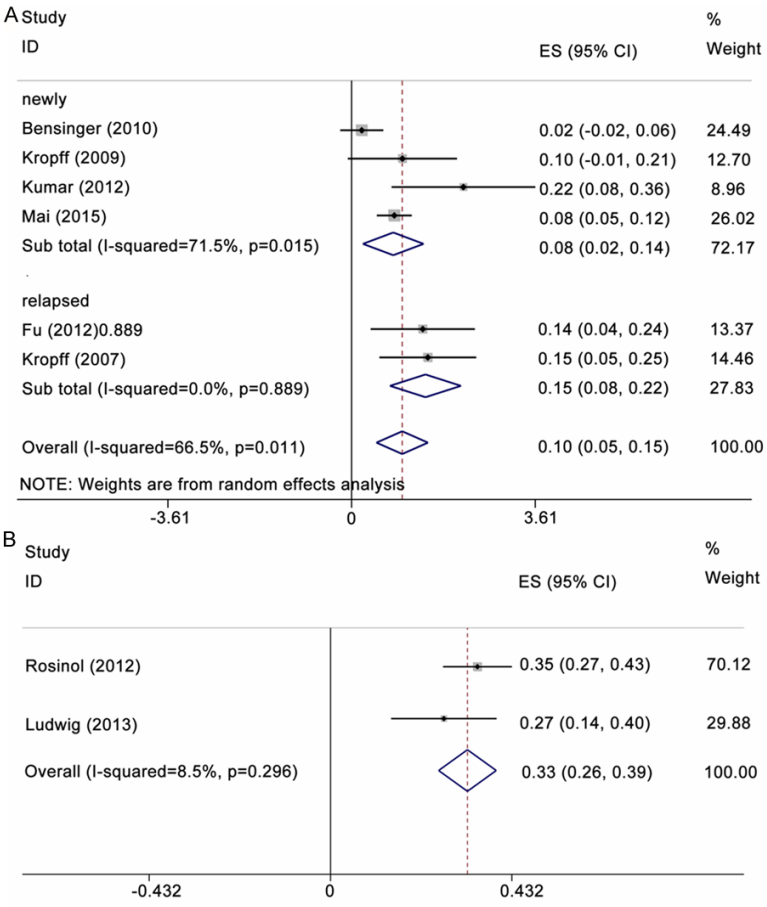

Figure 3. Evaluation of complete response with bortezomib-cyclophosphamide-dexamethasone (VCD) and bortezomib-thalidomide-dexamethasone (VTD) regimens for multiple myeloma treatment. A: Estimation with VCD regimen; B: Estimation with VTD regimen. ES: effect size; CI: confidence interval.

aforementioned agents. The ages were varied from 50 to 64. The detailed doses strategy is presented in **Table 2**. Given that only two studies involved the evaluation of VTDC, the pooled analysis of this regimen was not performed.

Outcomes of response

Four indexes such as PR, ORR, CR and VGPR were estimated in the meta-analysis. PR was defined as > 50% reduction of monoclonal immunoglobulin and > 90% reduction of light chain proteinuria; CR was defined as the complete disappearance of M protein in serum and urine on immunofixation and less than 5% bone marrow plasma cells. VGPR was defined as serum paraprotein reduction of > 90% and a 24 h urine M-protein excretion lower than 100 mg. ORR included all PR cases or better.

ORR

There were 8 studies with the VCD treatment reported ORR index, involving a total of 564 patients. Among them, two studies examined the relapsed MM. Due to remarkable heterogeneity was detected (I^2 = 79.8%, P = 0.000), a random-effects model was applied. The pooled results indicated that with the administration of VCD, the ORR for the newly diagnosed MM was 0.87 (95% CI: 0.80, 0.94), and was 0.789 (95% CI: 0.639, 0.886) for the relapsed MM (**Figure 2**), suggesting a more efficient effect of the administration of VCD on newly diagnosed MM than on relapsed MM patient. With regard to VTD treatment, two studies

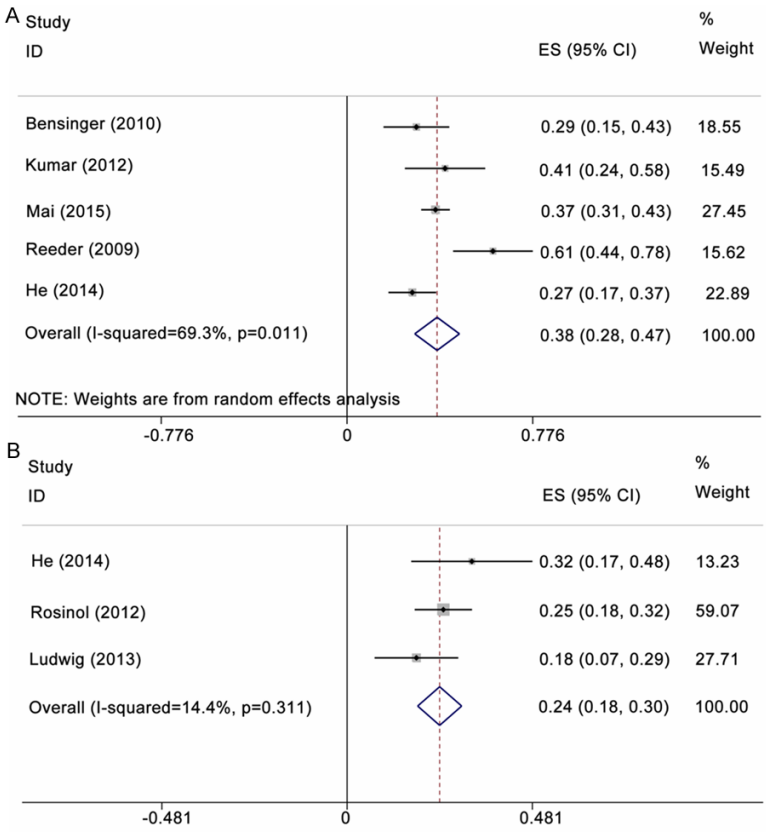

Figure 4. Evaluation of very good partial response with bortezomib-cyclophosphamide-dexamethasone (VCD) and bortezomib-thalidomide-dexamethasone (VTD) regimens for multiple myeloma treatment. A: Estimation with VCD regimen; B: Estimation with VTD regimen. ES: effect size; CI: confidence interval.

involved the evaluation of ORR, but only He and colleagues reported the available data, and ORR of the newly diagnosed MM was 0.853. Two studies evaluated the treatment of VTDC, and ORR was 0.96 for the newly diagnosed MM patients and 0.88 for the relapsed ones.

CR

There were 6 studies containing 454 patients reported CR in VCD treatment group, of which two studies were related to the relapsed MM. A random-effects model was used for the significant heterogeneity (I^2 = 66.5%, P = 0.011). As a result, the newly diagnosed MM applying the VCD treatment achieved a CR of 0.082 (95% CI: 0.022, 0.142), whereas the relapsed MM had a relatively higher CR of 0.145 (95% CI: 0.076, 0.215) (**Figure 3A**). Two studies involved the CR in the VTD group. For the absence of significant heterogeneity, a fixed-effects model was used to calculate the pooled result, which indicated that the CR for the newly diagnosed MM was 0.326 (95% CI: 0.257, 0.395) (**Figure 3B**). Comparing with VCD treatment, VTD had a remarkably increased CR (P = 0.039). In VTDC group, two studies examined the CR, with the values of 0.46 and 0.27, respectively for the newly diagnosed and relapsed MM.

VGPR

Five studies in the VCD group for newly diagnosed MM patients reported the VGPR, comprising of 436 cases. A random-effects model was applied for the detection of pronounced heterogeneity (I^2 = 69.3%, P = 0.011). The combined VGPR was 0.377 (95% CI: 0.283, 0.470) with VCD administration (**Figure 4A**). On the other hand, two studies in VTD group involved the evaluation of VGPR. For the obvious homogeneity (I^2 = 14.4%, P = 0.311), a fixed-effects model was selected and the pooled VGPR for newly diagnosed MM was 0.240 (95% CI: 0.183, 0.298) (**Figure 4B**). VTD treatment achieved a comparable effect on VGPR with VCD (P = 0.157). In the two studies of VTDC group, the VGPR for the newly diagnosed and relapsed MM patients were 0.25 and 0.09, respectively.

PR

In the 7 studies with the treatment of VCD that reported the PR, two were aimed at the relapsed MM patients. The total cases were 531 patients. A random-effects model was applied for the significant heterogeneity (I^2 = 95.0%, P = 0.000). The combined results indicated that PR was 0.461 (95% CI: 0.197, 0.726) for the newly diagnosed MM, and 0.601 (95% CI: 0.504, 0.698) for the relapsed MM (**Figure 5A**). For the two studies examining PR in the VTD group, a fixed-effects model was used to calculate the pooled PR, which was 0.284 (95% CI: 0.224, 0.344) for the newly diagnosed MM (**Figure**

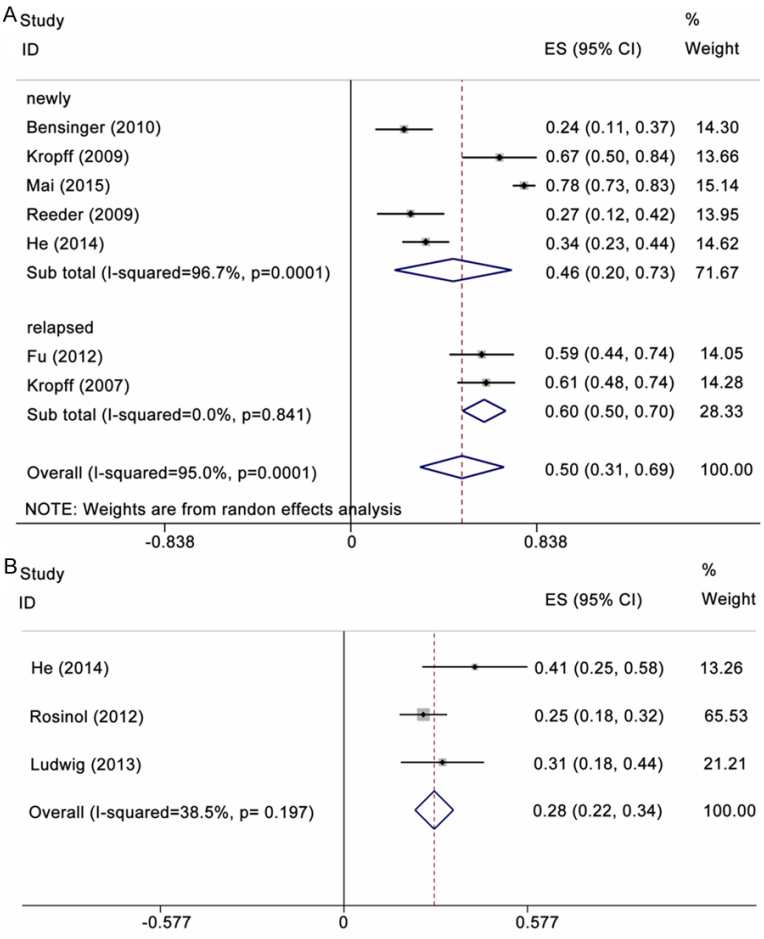

Figure 5. Evaluation of partial response with bortezomib-cyclophosphamide-dexamethasone (VCD) and bortezomib-thalidomide-dexamethasone (VTD) regimens for multiple myeloma treatment. A: Estimation with VCD regimen; B: Estimation with VTD regimen. ES: effect size; CI: confidence interval.

5B). There were also no significant differences between two treatment groups (P = 0.309). Referred to VTDC group, only two studies involved the VGPR assessment, with the value of 0.27 and 0.23, respectively for the newly diagnosed and relapsed MM patients.

Adverse events

Six toxicity indexes (grade ≥ 3) were evaluated, among which three were related to blood including thrombocytopenia, leukocytopenia and neutropenia; and three were irrelevant to blood such as fatigue, neuropathy and diarrhea.

Thrombocytopenia

Seven studies consisting of 520 cases reported the thrombocytopenia in VCD group, two of which were about the relapsed MM. A random-effects model was applied due to the prominent heterogeneity (I^2 = 90.6%, P = 0.016). As indicated in **Figure 6A**, the risk of thrombocytopenia for the newly diagnosed MM using VCD was 0.110 (95% CI: 0.041, 0.179), and for the relapsed MM was 0.338 (95% CI: -0.035, 0.710). In the VTD group, two studies involved the thrombocytopenia risk, and a fixed-effects model was selected to combine the result (I^2 = 40.9%, P = 0.184). As a result, the risk of thrombocytopenia was 0.083 (95% CI: 0.046, 0.120) for newly diagnosed MM with VTD treatment (**Figure 6B**). Significant differences between VCD and VTD on thrombocytopenia risk were not detected (P = 0.83). In the two studies treated with VTDC, the thrombocytopenia risks were 0.06 and 0.12, respectively for the newly diagnosed and relapsed MM patients.

Neutropenia

Three studies in the VCD group evaluated neutropenia. The participants were all newly diagnosed MM patients and the cases were 143. A fixed-effects model was used due to the significant homogeneity (I^2 = 35.0%, P = 0.215). VCD treatment achieved a neutropenia risk of 0.177 (95% CI: 0.115, 0.239) among the newly diagnosed MM patients (**Figure 7A**). With regard to VTD group, there were three studies reported the risk of neutropenia, and a fixed-effects model was selected (I^2 = 0.0%, P = 0.720). The pooled risk of neutropenia for the newly diagnosed MM was 0.112 (95% CI: 0.070, 0.154) (**Figure 7B**). The two treatments showed comparable effects on the risk of neutropenia (P = 0.232). In the two studies evaluated the neutropenia with the administration of VTDC, risk of neutropenia for the newly diagnosed MM was 0.18, and was 0.04 for the relapsed MM.

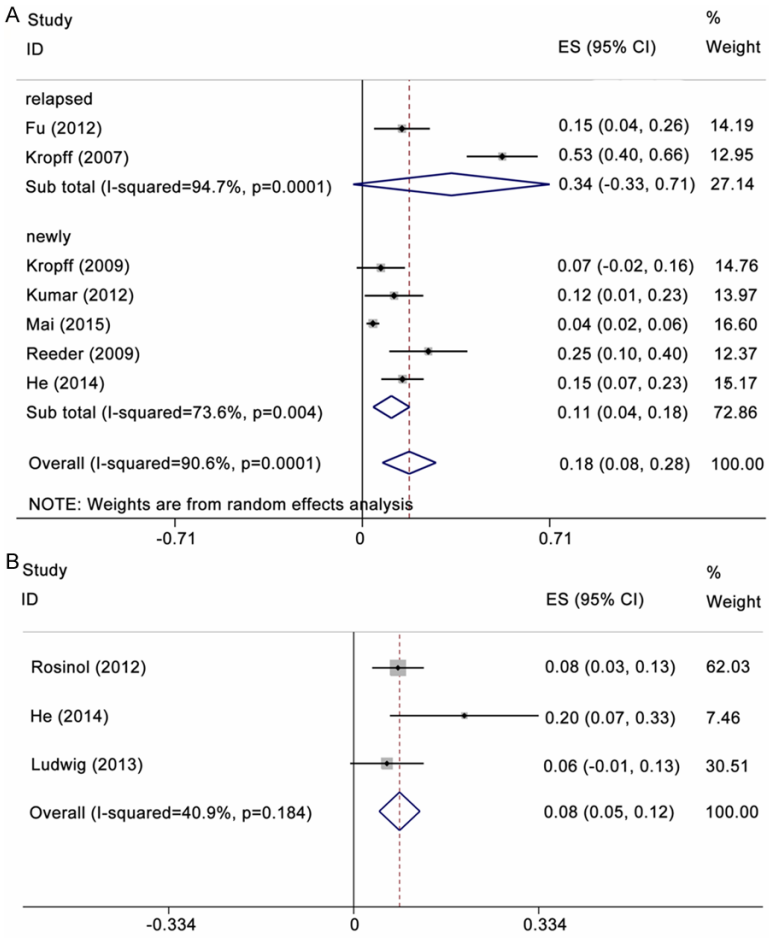

Figure 6. Evaluation of thrombocytopenia with bortezomib-cyclophosphamide-dexamethasone (VCD) and bortezomib-thalidomide-dexamethasone (VTD) regimens for multiple myeloma treatment. A: Estimation with VCD regimen; B: Estimation with VTD regimen. ES: effect size; CI: confidence interval.

Leukocytopenia

In the VCD treatment group, there were 3 studies concerned leukocytopenia. Among them, one was about the relapsed MM patients. The total cases were 116. Due to the detection of significant heterogeneity (I^2 = 84.4%, P = 0.002), a random-effects model was applied. The pooled results indicated that the risk of leukocytopenia for the newly diagnosed MM with VCD treatment was 0.267 (95% CI: -0.095, 0.629), while that for the relapsed MM was 0.2000 (95% CI: 0.092, 0.308) (**Figure 8A**).

Fatigue

Five studies involved fatigue in the VCD group, in which two were about the relapsed MM. There were 237 cases in this group and a fixed-effects model was used (I^2 = 70.8%, P = 0.032). As revealed in the pooled results, the risk of fatigue for the newly diagnosed MM with VCD agents was 0.181 (95% CI: 0.002, 0.361), and for the relapsed MM was 0.150 (95% CI: 0.054, 0.246) (**Figure 8B**).

Neuropathy

A set of six studies containing 443 cases in the VCD group concerned neuropathy. Among them, two were about the relapsed MM. A random-effects model was used (I^2 = 52.8%, P = 0.076). The risk of neuropathy for the newly diagnosed MM with VCD treatment was 0.072 (95% CI: 0.045, 0.099), and was 0.210 (95% CI: 0.100, 0.320) for the relapsed MM (**Figure 8C**).

Diarrhea

There were five studies in the VCD group reported diarrhea, with one referring to the relapsed MM. A cohort of 226 cases was involved in. The combined analysis was conducted under a random-effects model (I^2 = 66.5%, P = 0.018), and it was presented that the risk of diarrhea was 0.070 (95% CI: 0.008, 0.103) for the newly diagnosed MM, and 0.020 (95% CI: -0.018, 0.058) for the relapsed MM (**Figure 8D**).

Discussion

There was not a consistent assessment of the effects about VCD, VTD and VTDC on the MM patients, especially the relapsed MM. In the present meta-analysis, we included 11 studies to provide a comprehensive evaluation about the efficiency and safety of these treatments on MM patients. The results indicated that all the treatments achieved a higher response effect on the newly diagnosed MM than the relapsed MM. VCD and VTD had a comparable efficiency on the ORR, VGPR and PR. However, VTD had a pronounced higher CR than VCD on

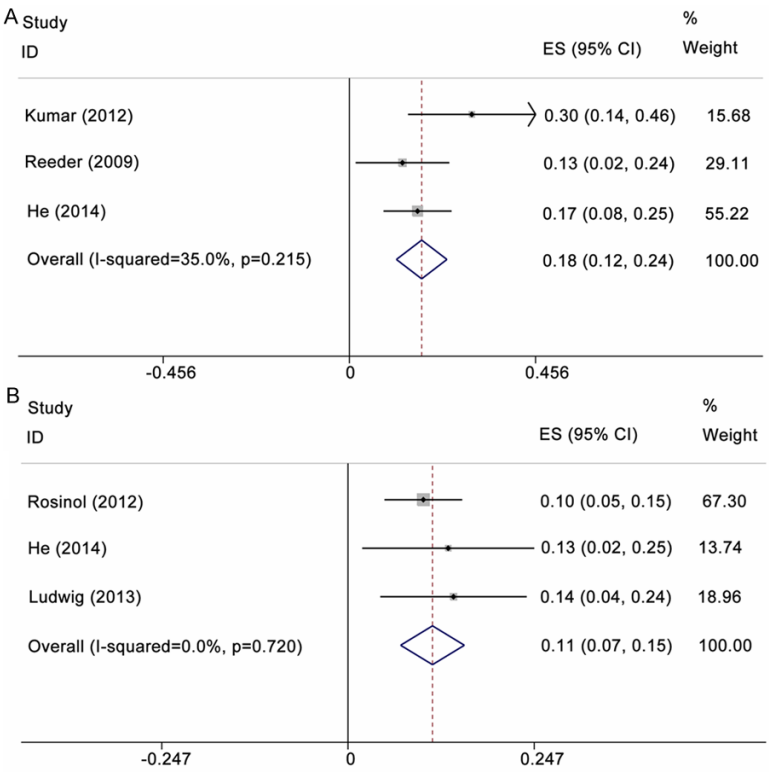

Figure 7. Evaluation of neuropathy with bortezomib-cyclophosphamide-dexamethasone (VCD) and bortezomib-thalidomide-dexamethasone (VTD) regimens for multiple myeloma treatment. A: Estimation with VCD regimen; B: Estimation with VTD regimen. ES: effect size; CI: confidence interval.

the newly diagnosed MM patients ($P < 0.05$). Notably, VTDC achieved a decreased risk of thrombocytopenia than either VCD or VTD (0.06 vs. 0.11 or 0.083) for the treatment of newly diagnosed MM. Besides, compared with VCD, VTD had a lower risk of thrombocytopenia (0.083 vs. 0.11) and neutropenia (0.112 vs. 0.177) for the newly diagnosed MM patients; however without statistical significance.

The increased response to MM therapy is tightly correlated with the improved long-term outcomes. The standard regimens of VCD and VTD have been confirmed both efficacious [19]. The synergetic enhancement of immunomodulatory drug thalidomide and the inhibitor bortezomib confers the improvement of clinical outcomes of MM patients [32]. The transcription factor nuclear factor-κB (NF-κB) acts as a crucial regulator in the inflammatory process of various cancer types, while the proteasome inhibitor bortezomib results in the stabilization of IκBβ, which could consequently decrease the NF-κB activity [33, 34]. Interestingly, it is well-elucidated that thalidomide suppressed the NF-κB activity via the inhibition of IκB kinase activity [35]. Additionally, the incorporation of both bortezomib and thalidomide contribute to the enhancement of dexamethasone activity [36]. These might be the reasonable explanations of the better efficiency of the administration of VTD. Moreover, VTD is verified to be a potent non-chemotherapeutic drug that causes pronounced reduction of tumor cell in patients with autografted myeloma by RQ-PCR [37]. As expected, our results indicated that VTD attained a significant higher CR than VCD with regard to CR (0.326 vs. 0.082), supporting the superiority of VTD regimen for the newly diagnosed MM. Given that cyclophosphamide is beneficial for the collection and transplantation of stem cells, it is understandable that the four-drug combination of VTDC achieved a more increased CR than VTD (0.46 vs. 0.326).

In the present study, VCD presented a comparable effect with VTD regarding to ORR, VGPR and PR, inconsistent with previous findings that VTD is more advantageous than VCD [19, 31]. The possible causative factors might be that only two studies examining the VTD effectiveness were included in our meta-analysis; and moreover, due to the finite available information, we did not calculate the pooled results, which might cause the deviation of the results. Besides, there lacked the phase III clinical data.

As MM is a progressive disease, most patients suffered with MM would inevitably undergo the relapse after the remission of drug therapy. Due to the individual difference, the time to relapse of different patients is quite variable [38], which might account for the lower ORR among the relapsed MM, comparing with that among the newly diagnosed MM patients, with both VCD regimen and VTDC regimen (0.789

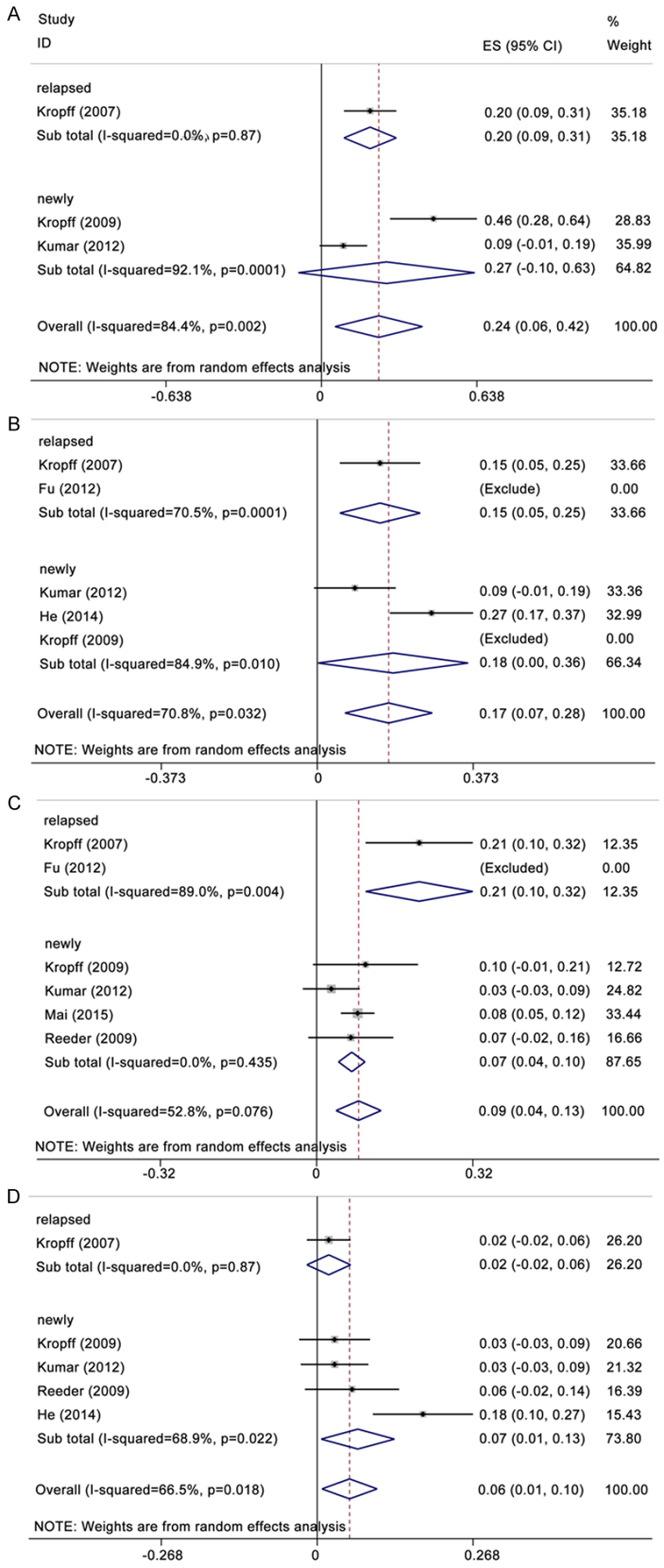

Figure 8. Evaluation of other adverse effects with thrombocytopenia with bortezomib-cyclophosphamide-dexamethasone (VCD) regimen for multiple myeloma treatment. A: Evaluation of leukocytopenia; B: Evaluation of fatigue; C: Evaluation of neuropathy; D: Evaluation of diarrhea. ES: effect size; CI: confidence interval.

vs. 0.87, and 0.88 vs. 0.96, respectively). Another plausible factor might be that only a small portion of the included studies explored the relapsed patients with MM, which might bring in bias of the results.

On the other hand, VTD also exhibited a well-tolerant toxicity such as a decreased risk of thrombocytopenia and neutropenia, compared with VCD (0.083 vs. 0.11 and 0.112 vs. 0.177, respectively, though without significance). In spite of the remarkable higher risk of grade 3-4 neurotoxicity (62% vs. 27%) comparing with VCD therapy, VTD achieves a lower overall adverse events (6% vs. 11%) [19], suggesting that VTD had a more tolerance than VCD. The putative explanation is thatbortezomib-induced peripheral neuropathy might be deducted by the anti-inflammatory effects of thalidomide [16]. With regard to the comparison of three-drug regimen and four-drug regimen, though VTD presentes a similar CR and ORR with VTDC and hence is considered as effective as VTDC regimen, the rates of toxicity with VTDC is higher than that with VTD [39], consisting with our findings that the risk of neutropenia with VTD was 0.112, while was 0.18 with VTDC, for the newly diagnosed MM patients.

Despite the advantages that our meta-analysis contained

more relevant studies and that subgroup analysis stratified by MM types was considered, several limitations of this study should be discussed. Though we performed the subgroup analysis, different types were not well-distributed in the studies, and the relapsed MM was not mentioned in the VTD regimen. Moreover, substantial heterogeneity across studies was observed in the VCD group, which might distort the combined results. Importantly, only two studies involved the evaluation of VTDC, which might provide the inaccurate results to some extent. Therefore more large numbers of randomized controlled trials (RCTs) and the validations in stage III trials are warranted.

In conclusion, our findings indicated that for newly diagnosed MM patients, VTD had a comparable effectiveness with VCD in terms of ORR, VGPR and PR, but a pronounced higher CR than VCD. Moreover, VTD was more well-tolerant than VCD. Besides, VTDC had increased CR and also achieved higher risk of toxicity, comparing with VTD. However, more RCTs with large sample size are needed to confirm these findings.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Lihong Shou, Department of Hematology, Huzhou Central Hospital, Huzhou 313000, Zhejiang, China. Tel: +86-572-2023301-2191; Fax: +86-572-2023301-6625; E-mail: lihongshoulhs@163.com

References

[1] Kumar SK, Rajkumar SV, Dispenzieri A, Lacy MQ, Hayman SR, Buadi FK, Zeldenrust SR, Dingli D, Russell SJ and Lust JA. Improved survival in multiple myeloma and the impact of novel therapies. Blood 2008; 111: 2516-2520.

[2] Noll JE, Williams SA, Tong CM, Wang H, Quach JM, Purton LE, Pilkington K, To LB, Evdokiou A and Gronthos S. Myeloma plasma cells alter the bone marrow microenvironment by stimulating the proliferation of mesenchymal stromal cells. Haematologica 2014; 99: 163-171.

[3] Becker N. Epidemiology of multiple myeloma. In: editors. Multiple Myeloma. Springer; 2011. pp. 25-35.

[4] Shimizu K. Clinical features of multiple myeloma. Nihon rinsho 2007; 65: 2218-2222.

[5] Lamm W, Eder S, Bojic M, Zielinski CC and Drach J. Novel agents have a significant impact on survival of patients with multiple myeloma. Wien Klin Wochenschr 2015; 127: 92-7.

[6] Cook G, Williams C, Brown JM, Cairns DA, Cavenagh J, Snowden JA, Ashcroft AJ, Fletcher M, Parrish C and Yong K. High-dose chemotherapy plus autologous stem-cell transplantation as consolidation therapy in patients with relapsed multiple myeloma after previous autologous stem-cell transplantation (NCRI Myeloma X Relapse [Intensive trial]): a randomised, open-label, phase 3 trial. Lancet Oncol 2014; 15: 874-885.

[7] Kropff M, Vogel M, Kreter A, Schlag R, Müller L, Weide R, Knauf W, Decker T, Fiechtner H and Kojouharoff G. Bortezomib and Low-Dose Dexamethasone with or without Continuous Low-Dose Oral Cyclophosphamide for Primary Refractory or Relapsed Multiple Myeloma: Final Results of a National Multicenter Randomized Controlled Phase III Study. Blood 2014; 124: 3470-3470.

[8] Oakervee HE, Popat R, Curry N, Smith P, Morris C, Drake M, Agrawal S, Stec J, Schenkein D and Esseltine DL. PAD combination therapy (PS-341/bortezomib, doxorubicin and dexamethasone) for previously untreated patients with multiple myeloma. Brit J Haematol 2005; 129: 755-762.

[9] Barlogie B, Shaughnessy J, Tricot G, Jacobson J, Zangari M, Anaissie E, Walker R and Crowley J. Treatment of multiple myeloma. Blood 2004; 103: 20-32.

[10] Kim YK, Sohn SK, Lee JH, Yang DH, Moon JH, Ahn JS, Kim HJ, Lee JJ; Korean Multiple Myeloma Working Party (KMMW). Clinical efficacy of a bortezomib, cyclophosphamide, thalidomide, and dexamethasone (Vel-CTD) regimen in patients with relapsed or refractory multiple myeloma: a phase II study. Ann Hematol 2010; 89: 475-482.

[11] García-Sanz R, González-López T, Vázquez L, Hermida G, Graciani I and San Miguel J. The combination of thalidomide, cyclophosphamide and dexamethasone is potentially useful in highly resistant Hodgkin's lymphoma. Eur J Haematol 2010; 84: 266-270.

[12] Rajkumar SV, Blood E, Vesole D, Fonseca R and Greipp PR. Phase III clinical trial of thalidomide plus dexamethasone compared with dexamethasone alone in newly diagnosed multiple myeloma: a clinical trial coordinated by the Eastern Cooperative Oncology Group. J Clin Oncol 2006; 24: 431-436.

[13] Reeder C, Reece DE, Kukreti V, Chen C, Trudel S, Hentz J, Noble B, Pirooz NA, Spong JE and Piza JG. Cyclophosphamide, bortezomib and dexamethasone induction for newly diagnosed

multiple myeloma: high response rates in a phase II clinical trial. Leukemia 2009; 23: 1337-1341.
[14] Mai E, Bertsch U, Dürig J, Kunz C, Haenel M, Blau I, Munder M, Jauch A, Schurich B and Hielscher T. Phase III trial of bortezomib, cyclophosphamide and dexamethasone (VCD) versus bortezomib, doxorubicin and dexamethasone (PAd) in newly diagnosed myeloma. Leukemia 2015; 29: 1721-9.
[15] Moreau P, Avet-Loiseau H, Facon T, Attal M, Tiab M, Hulin C, Doyen C, Garderet L, Randriamalala E and Araujo C. Bortezomib plus dexamethasone versus reduced-dose bortezomib, thalidomide plus dexamethasone as induction treatment before autologous stem cell transplantation in newly diagnosed multiple myeloma. Blood 2011; 118: 5752-5758.
[16] Cavo M, Pantani L, Petrucci MT, Patriarca F, Zamagni E, Donnarumma D, Crippa C, Boccadoro M, Perrone G and Falcone A. Bortezomib-thalidomide-dexamethasone is superior to thalidomide-dexamethasone as consolidation therapy after autologous hematopoietic stem cell transplantation in patients with newly diagnosed multiple myeloma. Blood 2012; 120: 9-19.
[17] He J, Yang L, Han X, Zheng G, Zheng W, Wei G, Wu W, Ye X, Shi J and Xie W. The Choice of Regimens Based on Bortezomib for Patients with Newly Diagnosed Multiple Myeloma. PLoS One 2014; 9: e99174.
[18] Kumar S, Flinn IW, Richardson PG, Hari P, Callander NS, Noga SJ, Stewart AK, Glass J, Rifkin RM, Wolf JL. Novel three-and four-drug combination regimens of bortezomib, dexamethasone, cyclophosphamide, and lenalidomide, for previously untreated multiple myeloma: results from the multi-center, randomized, phase 2 EVOLUTION study. In: ASH Annual Meeting Abstracts: 2010; 2010: 621.
[19] Leiba M, Kedmi M, Duek A, Freidman T, Weiss M, Leiba R, Nagler A and Avigdor A. Bortezomib-Cyclophosphamide-Dexamethasone (VCD) versus Bortezomib-Thalidomide-Dexamethasone (VTD)-based regimens as induction therapies in newly diagnosed transplant eligible patients with multiple myeloma: a meta-analysis. Brit J Haematol 2014; 166: 702-710.
[20] Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg 2010; 8: 336-341.
[21] Higgins J and Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002; 21: 1539-1558.
[22] Sedgwick P. Independent samples t test. BMJ 2010; 340.
[23] Ben Q, Xu M, Ning X, Liu J, Hong S, Huang W, Zhang H and Li Z. Diabetes mellitus and risk of pancreatic cancer: a meta-analysis of cohort studies. Eur J Cancer 2011; 47: 1928-1937.
[24] Uhlemann M, Möbius-Winkler S, Mende M, Eitel I, Fuernau G, Sandri M, Adams V, Thiele H, Linke A and Schuler G. The Leipzig prospective vascular ultrasound registry in radial artery catheterization: impact of sheath size on vascular complications. JACC-Cardiovasc Inte 2012; 5: 36-43.
[25] Bensinger WI, Jagannath S, Vescio R, Camacho E, Wolf J, Irwin D, Capo G, McKinley M, Potts P and Vesole DH. Phase 2 study of two sequential three-drug combinations containing bortezomib, cyclophosphamide and dexamethasone, followed by bortezomib, thalidomide and dexamethasone as frontline therapy for multiple myeloma. Brit J Haematol 2010; 148: 562-568.
[26] Fu W, Delasalle K, Wang J, Song S, Hou J, Alexanian R and Wang M. Bortezomib-cyclophosphamide-dexamethasone for relapsing multiple myeloma. Am J Clin Oncol 2012; 35: 562-565.
[27] Kropff M, Bisping G, Schuck E, Liebisch P, Lang N, Hentrich M, Dechow T, Kröger N, Salwender H and Metzner B. Bortezomib in combination with intermediate-dose dexamethasone and continuous low-dose oral cyclophosphamide for relapsed multiple myeloma. Brit J Haematol 2007; 138: 330-337.
[28] Kropff M, Liebisch P, Knop S, Weisel K, Wand H, Gann CN, Berdel WE and Einsele H. DSMM XI study: dose definition for intravenous cyclophosphamide in combination with bortezomib/dexamethasone for remission induction in patients with newly diagnosed myeloma. Ann Hematol 2009; 88: 1125-1130.
[29] Kumar S, Flinn I, Richardson PG, Hari P, Callander N, Noga SJ, Stewart AK, Turturro F, Rifkin R and Wolf J. Randomized, multicenter, phase 2 study (EVOLUTION) of combinations of bortezomib, dexamethasone, cyclophosphamide, and lenalidomide in previously untreated multiple myeloma. Blood 2012; 119: 4375-4382.
[30] Messeguer M, de Salamanca CU, de Octubre UD and La Princesa U. Superiority of bortezomib, thalidomide, and dexamethasone (VTD) as induction pretransplantation therapy in multiple myeloma: a randomized phase 3 PETHEMA/GEM study. Blood 2012; 120: 1589-1596.
[31] Ludwig H, Viterbo L, Greil R, Masszi T, Spicka I, Shpilberg O, Hajek R, Dmoszynska A, Paiva B and Vidriales MB. Randomized phase II study

of bortezomib, thalidomide, and dexamethasone with or without cyclophosphamide as induction therapy in previously untreated multiple myeloma. J Clin Oncol 2013; 31: 247-255.
[32] Attal M, Lauwers-Cances V, Marit G, Caillot D, Moreau P, Facon T, Stoppa AM, Hulin C, Benboubker L and Garderet L. Lenalidomide maintenance after stem-cell transplantation for multiple myeloma. N Engl J Med 2012; 366: 1782-1791.
[33] DiDonato JA, Mercurio F and Karin M. NF-κB and the link between inflammation and cancer. Immunol Rev 2012; 246: 379-400.
[34] Strauss SJ, Maharaj L, Hoare S, Johnson PW, Radford JA, Vinnecombe S, Millard L, Rohatiner A, Boral A and Trehu E. Bortezomib therapy in patients with relapsed or refractory lymphoma: potential correlation of in vitro sensitivity and tumor necrosis factor alpha response with clinical activity. J Clin Oncol 2006; 24: 2105-2112.
[35] Keifer JA, Guttridge DC, Ashburner BP and Baldwin AS. Inhibition of NF-κB activity by thalidomide through suppression of IκB kinase activity. J Biol Chem 2001; 276: 22382-22387.
[36] Mitsiades N, Mitsiades CS, Poulaki V, Chauhan D, Richardson PG, Hideshima T, Munshi NC, Treon SP and Anderson KC. Apoptotic signaling induced by immunomodulatory thalidomide analogs in human multiple myeloma cells: therapeutic implications. Blood 2002; 99: 4525-4530.
[37] Ladetto M, Pagliano G, Ferrero S, Cavallo F, Drandi D, Santo L, Crippa C, De Rosa L, Pregno P and Grasso M. Major tumor shrinking and persistent molecular remissions after consolidation with bortezomib, thalidomide, and dexamethasone in patients with autografted myeloma. J Clin Oncol 2010; 28: 2077-2084.
[38] Lonial S. Relapsed multiple myeloma. ASH Education Program Book 2010; 2010: 303-309.
[39] Ludwig H, Viterbo L, Greil R, Masszi T, Spicka I, Shpilberg O, Hajek R, Dmoszynska A, Cakana A, Enny C. Bortezomib, Thalidomide, and Dexamethasone (VTD) Versus VTD Plus Cyclophosphamide as Induction Therapy in Previously Untreated Multiple Myeloma Patients Eligible for HDT-ASCT: A Randomized Phase 2 Trial. In: ASH Annual Meeting Abstracts: 2009; 2009: 2312.