

Original Article

Single-agent bortezomib or bortezomib-based regimens as consolidation therapy after autologous hematopoietic stem cell transplantation in multiple myeloma: a meta-analysis of randomized controlled trials

Minjie Gao^{1*}, Guang Yang^{1*}, Ying Han^{1*}, Yuanyuan Kong¹, Huiqun Wu¹, Yi Tao¹, Fenghuang Zhan², Jumei Shi¹, Xiaosong Wu¹

¹Department of Hematology, Shanghai Tenth People's Hospital, Tongji University School of Medicine, Shanghai, China; ²Department of Internal Medicine, University of Iowa, Carver College of Medicine, Iowa, USA. *Equal contributors.

Received March 7, 2015; Accepted May 28, 2015; Epub August 15, 2015; Published August 30, 2015

Abstract: The efficacy and safety of single-agent bortezomib or bortezomib-based regimens as consolidation therapy after autologous hematopoietic stem cell transplantation (ASCT) in patients with multiple myeloma (MM) has been in question. To address the issue, we conducted a meta-analysis of two randomized double-blind placebo-controlled studies involving a total of 691 patients. The primary outcomes of interest were progression-free survival (PFS) and response rate. Secondary outcomes included overall survival (OS) and adverse events. There was a marked benefit in 3-year PFS with bortezomib (Odds Ratio [OR] = 1.52, 95% confidence interval [CI] = 1.11 to 2.08), whereas there was no difference in 3-year overall survival (OS; OR = 0.91, 95% CI = 0.60 to 1.37). More bortezomib-treated patients achieved at least a very good partial response (\geq VGPR) (OR = 1.73, 95% CI = 1.19 to 2.51). The rate of complete response or near-complete response (CR/nCR) was significantly higher with bortezomib consolidation therapy (OR = 1.62, 95% CI = 1.18 to 2.22). For adverse events, more patients in the bortezomib consolidation therapy arm experienced peripheral neuropathy (OR = 4.03, 95% CI = 2.72 to 5.96). Significant differences were also seen with those experiencing peripheral neuropathy greater than grade 2 (OR = 4.26, 95% CI = 1.06 to 17.11). Based on these results, we conclude that single-agent bortezomib or bortezomib-based regimens as consolidation therapy after ASCT in patients with MM was effective in the improvement of PFS and response rate. However, peripheral neuropathy must be closely monitored.

Keywords: Bortezomib, multiple myeloma, consolidation therapy, meta-analysis

Introduction

High-dose therapy plus autologous stem cell transplantation (ASCT) has improved overall survival (OS) for patients with multiple myeloma (MM) over the last decade and remains the standard of care for patients 65 years of age or younger [1-4]. The proteasome inhibitor bortezomib-based regimen has been shown to be very efficacious as an induction therapy before ASCT [5-8]. The success of bortezomib before ASCT led to its use as a consolidation and maintenance therapy after ASCT [9, 10]. Although the terms consolidation and maintenance are often used synonymously in the

transplant setting, the two terms are distinct. Maintenance therapy is long-term and aims to decrease the risk of relapse [11], whereas consolidation therapy is short-term to enhance the response of the prior treatment phases, which could include novel agent-based induction therapy and ASCT [11-13]. Because results have been inconsistent across several studies [14-19], the role of consolidation and maintenance therapy is still unclear for patients with MM [13].

The primary aim of our study was to evaluate, in retrospect, whether the addition of single-agent bortezomib or bortezomib-based regimens as

Bortezomib therapy for myeloma

Table 1. Search criterion of medline (via pubmed, from inception to September 30, 2014)

No.	Query results	Results
#5	Search ((((((“Randomized Controlled Trials as Topic”[Mesh]) OR “Randomized Controlled Trial” [Publication Type])) AND ((consolidation [Title/Abstract]) OR “Consolidation Chemotherapy” [Mesh])) AND ((((((myeloma [Title/Abstract]) OR myelom* [Title/Abstract]) OR multiple myeloma [Title/Abstract]) OR plasmacytoma [Title/Abstract]) OR plasmocytom* [Title/Abstract]) OR “Plasmacytoma” [Mesh])) AND ((bortezomib [Title/Abstract]) OR “bortezomib” [Supplementary Concept]))	15
#4	Search (“Randomized Controlled Trials as Topic” [Mesh]) OR “Randomized Controlled Trial” [Publication Type]	460490
#3	Search (bortezomib [Title/Abstract]) OR “bortezomib” [Supplementary Concept]	5110
#2	Search (consolidation [Title/Abstract]) OR “Consolidation Chemotherapy” [Mesh]	19054
#1	Search ((((((myeloma [Title/Abstract]) OR myelom*[Title/Abstract]) OR multiple myeloma [Title/Abstract]) OR plasmacytoma [Title/Abstract]) OR plasmocytom* [Title/Abstract]) OR “Plasmacytoma” [Mesh])	54808

#represent number; *represent one or more letters of the alphabet.

Table 2. Search criterion of cochrane library (from inception to September 30, 2014)

No.	Query Results	Results
#1	“myeloma”: ti, ab, kw or “myeloma*”: ti, ab, kw or “multiple myeloma”: ti, ab, kw or “plasmacytoma”: ti, ab, kw or “plasmocytom*”: ti, ab, kw (Word variations have been searched)	2041
#2	MeSH descriptor: [multiple myeloma] explode all trees	879
#3	#1 or #2	2041
#4	“consolidation”: ti, ab, kw (Word variations have been searched)	1419
#5	MeSH descriptor: [consolidation chemotherapy] explode all trees	21
#6	#4 or #5	1419
#7	“bortezomib”: ti, ab, kw or “Velcade”: ti, ab, kw or LDP-341: ti, ab, kw or PS 341: ti, ab, kw or PS-341: ti, ab, kw (Word variations have been searched)	338
#8	#3 and #6 and #7	15

#represent number; *represent one or more letters of the alphabet.

Bortezomib therapy for myeloma

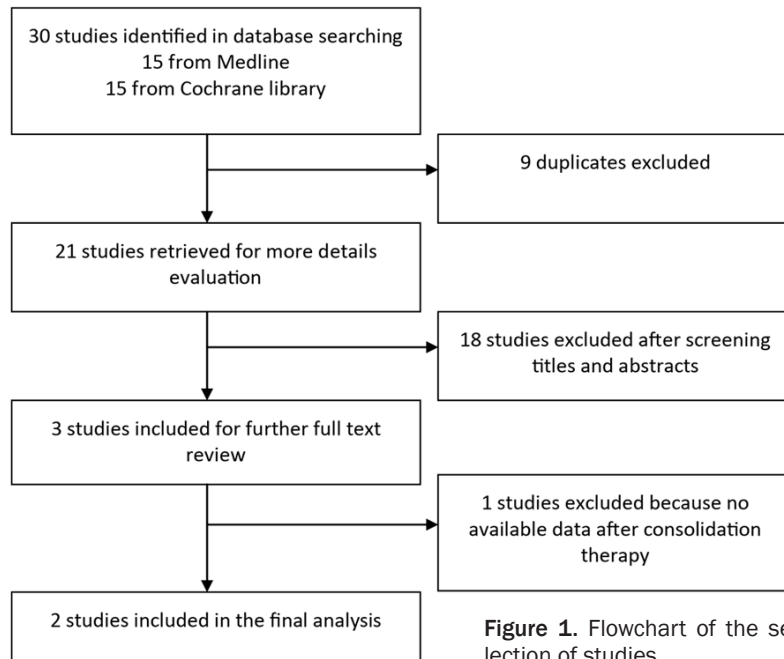


Figure 1. Flowchart of the selection of studies.

Selection criteria

Only phase 3 RCTs that compared single-agent bortezomib or bortezomib-based regimens with placebo controls as consolidation therapy after ASCT for patients with MM were included. Reports had to include the treatment strategy, the criteria used for selecting patients, and clinical outcomes or safety of the treatments. The eligibility of each study was assessed independently by two investigators.

Data extraction and methodological quality assessment

consolidation therapy would improve clinical outcomes. After review of the current literature, we identified two phase 3 randomized controlled trials (RCTs) that assessed the efficacy and safety of single-agent bortezomib or bortezomib-based regimens as consolidation therapy after ASCT in patients with MM [12, 13]. We then conducted a meta-analysis of these trials in an attempt to clarify the relative benefits and risks of single-agent bortezomib or bortezomib-based regimens as consolidation therapy after ASCT in patients with MM. Progression-free survival (PFS) and response rate were the two primary outcomes for this meta-analysis, and OS and adverse events were secondary outcomes.

Methods

Search strategy

We used MEDLINE and the Cochrane Library to locate all relevant studies published up to September 2014. The search criteria are listed in **Tables 1**, and **2**. 'The related articles' function in PubMed to identify other potentially relevant articles was used. Further, the ClinicalTrials.gov registry was searched. All the references of retrieved articles were also evaluated. Data was collected only from published, peer-reviewed papers.

The quality of trials was evaluated by two independent reviewers, who examined the adequacy of the allocation generation, allocation concealment, double blinding, data analysis, and power analysis. Data extraction was performed independently based on selection criteria. If a disagreement arose between the reviewers, agreement was achieved through consultation with a third reviewer.

Statistical analysis

For each trial, the effect of consolidation treatment was expressed as an Odds Ratio [OR] with 95% confidence interval [CI]. Both the fixed effects model and random effects model were used to calculate the pooled OR. Heterogeneity was assessed by both the chi-squared test and I^2 statistics. Statistically significant heterogeneity was considered as $P < 0.1$ or I^2 statistics $> 50\%$. The random effects model was selected when heterogeneity was significant. Revman software (5.2) was used to perform all calculations.

Results

Selection of the trials

Our initial search yielded 30 potential relevant studies, of which nine studies were duplicated and 18 studies were deemed ineligible after

Bortezomib therapy for myeloma

Table 3. Characteristics of studies fulfilling inclusion criteria in the meta-analysis

Author [Year]	Inclusion criteria	No. of patients (% of male)	Age, mean	Therapy
Cavo [2012]	18 to 65 years Previously untreated MM	VTD:160 (60) TD:161 (59)	VTD:55.6 TD:55.5	VTD (V 1.3 mg/m ² d1, 8, 15, 22, T 100 mg/d, D 40 mg d1, 2, 8, 9, 15, 16, 22, 23); TD (T 100 mg/d, D 40 mg d1-4, 20-23)
Mellqvist [2013]	V naïve; No progression in the first 3 months After ASCT	V:187 (59) P:183 (60)	V:59.1 P:58.7	First 2 cycles: V 1.3 mg/m ² d1, 4, 8, 11 for 3 w; Next 4 cycles: V 1.3 mg/m ² d1, 8, 15 for 4 w

MM: multiple myeloma; V: bortezomib; T: thalidomide; D: dexamethasone; P: placebo; ASCT: autologous stem cell transplantation; d: day; w: week.

Table 4. Methodological quality assessment of included trials

Author [Year]	Location	Allocation generation	Allocation concealment	Double blinding	Data analysis	Power analysis
Cavo [2012]	Italy	Unclear	Unclear	Double blinded	PP	Yes
Mellqvist [2013]	Denmark, Estonia, Finland, Iceland, Norway, Sweden	Computer generated	Unclear	Double blinded	ITT	Yes

ITT: intention-to-treat; PP: per-protocol.

Bortezomib therapy for myeloma

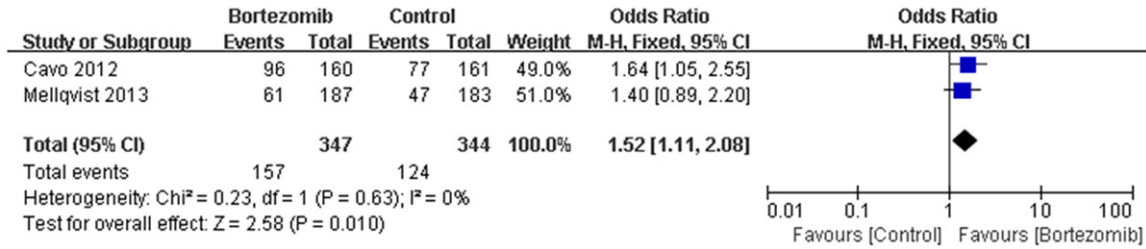


Figure 2. Pooled odd ratios of progression-free survival in the comparison of single-agent bortezomib or bortezomib-based regimens and placebo controls as consolidation therapy.

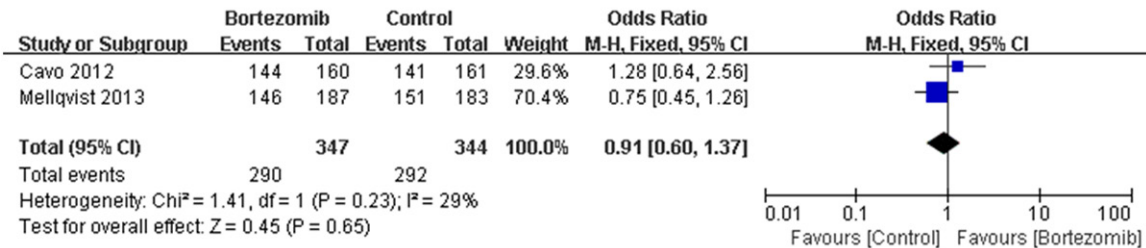


Figure 3. Pooled odd ratios of overall survival in the comparison of single-agent bortezomib or bortezomib-based regimens and placebo controls as consolidation therapy.

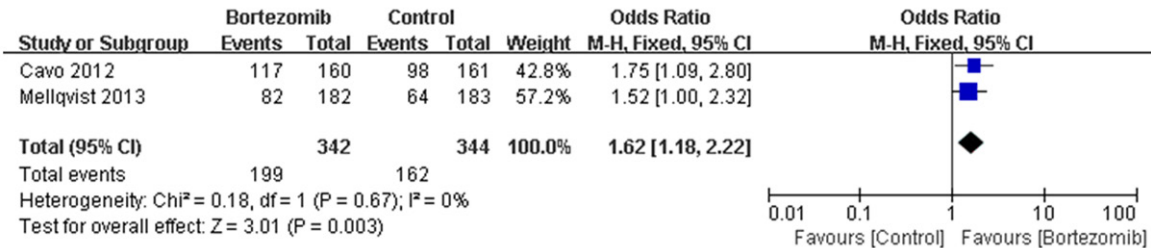


Figure 4. Pooled odd ratios of complete response or near-complete response in the comparison of single-agent bortezomib or bortezomib-based regimens and placebo controls as consolidation therapy.

screening titles and abstracts (**Figure 1**). The full text of the remaining 3 studies was reviewed in full, revealing two randomized controlled trials that fully met the inclusion criteria [12, 13]. One trial was excluded because no data regarding consolidation outcomes were available as defined by our inclusion criteria [20].

Description of trials

An outline of the two trials is provided in **Table 3**, and their methodological quality is summarized in **Table 4**. The trial results were published between 2012 and 2013. Both reported the efficacy and safety of single-agent bortezomib or bortezomib-based regimens as consolidation therapy after ASCT in patients with MM, were double blinded, and described power

analysis. Mellqvist et al. used intention-to-treat analysis and described the methods of allocation generation. Cavo et al. used per-protocol analysis and did not report the methods of allocation generation. Neither trial described the methods of allocation concealment.

Survival

From the two trials, 691 patients were evaluable for PFS. The pooled OR of PFS was 1.52 (95% CI = 1.11 to 2.08, P = 0.01), showing marked benefit of bortezomib consolidation for improving PFS, with no statistically significant heterogeneity (P = 0.63, I² = 0%, **Figure 2**). Both trials were eligible for analysis of OS (691 patients). There was no statistically significant difference in OS between the arms (OR = 0.91,

Bortezomib therapy for myeloma

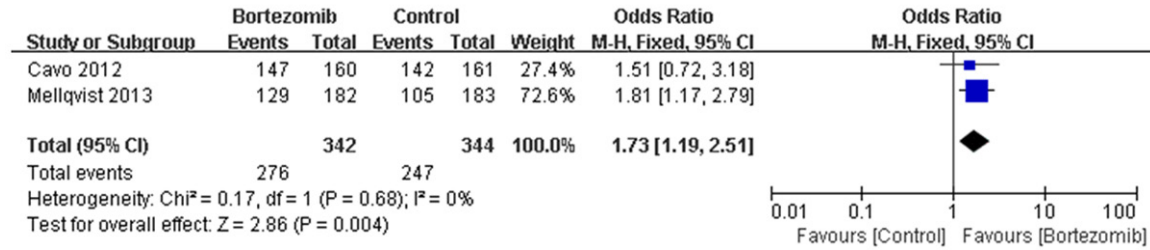


Figure 5. Pooled odd ratios of at least very good partial response in the comparison of single-agent bortezomib or bortezomib-based regimens and placebo controls as consolidation therapy.

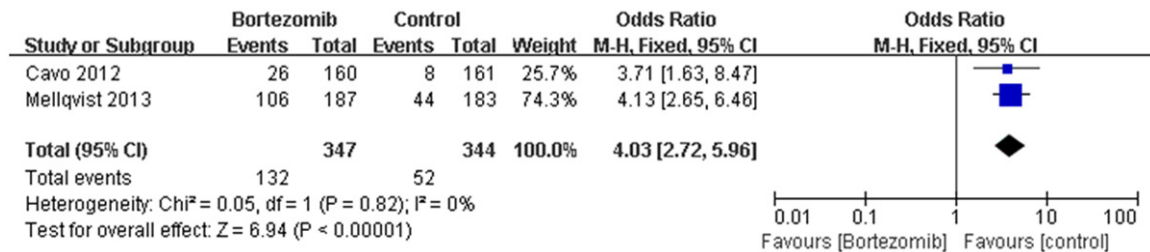


Figure 6. Pooled odd ratios of peripheral neuropathy in the comparison of single-agent bortezomib or bortezomib-based regimens and placebo controls as consolidation therapy.

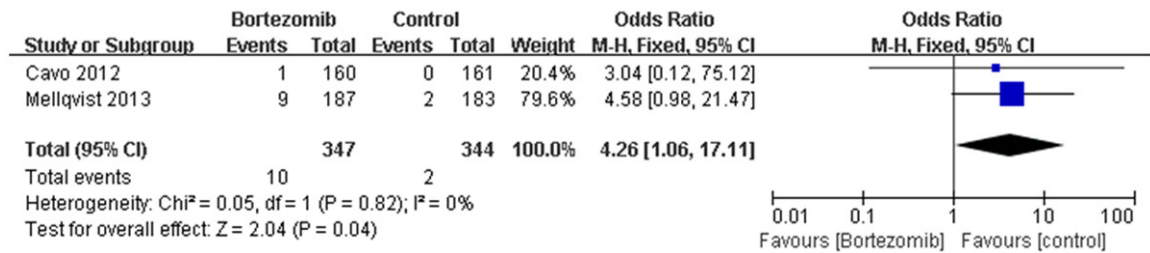


Figure 7. Pooled odd ratios of peripheral neuropathy > grade 2 in the comparison of single-agent bortezomib or bortezomib-based regimens and placebo controls as consolidation therapy.

95% CI = 0.60 to 1.37, P = 0.65). Heterogeneity for OS was not significant between the two trials (P = 0.23, I² = 29%, **Figure 3**).

Response rate

In the bortezomib and placebo arms, 342 and 344 patients were evaluable for response rate, respectively. There were 199 patients achieving complete response or near-complete response (CR/nCR) in the bortezomib arm and 162 patients achieving CR/nCR in the placebo arm. As shown in **Figure 4**, there was a significant difference in CR/nCR between the two arms (OR = 1.62, 95% CI = 1.18 to 2.22). No heterogeneity was observed (P = 0.67, I² = 0%). 276 patients achieved at least a very good par-

tial response (VGPR) in the bortezomib arm, and 247 patients achieved at least VGPR in the placebo arm. There was a significant difference in at least VGPR between the two arms (OR = 1.73, 95% CI = 1.19 to 2.51). No heterogeneity was observed (P = 0.68, I² = 0%, **Figure 5**).

Adverse events

Among all the adverse events, the incidence of peripheral neuropathy was reported in both trials. As shown in **Figure 6**, we found significant differences between bortezomib and placebo arms, with more patients in the bortezomib arm experiencing greater incidence of peripheral neuropathy (OR = 4.03, 95% CI = 2.72 to 5.96). Significant differences were also seen with

peripheral neuropathy greater than (>) grade 2 (OR = 4.26, 95% CI = 1.06 to 17.11, **Figure 7**). Heterogeneity was not significant for peripheral neuropathy ($P = 0.82$, $I^2 = 0\%$).

Discussion

The efficacy and safety of single-agent bortezomib or bortezomib-based regimens as consolidation therapy after autologous hematopoietic stem cell transplantation (ASCT) in patients with MM has been in question. In order to address the issue, we conducted a meta-analysis of two randomized double-blinded placebo-controlled studies encompassing 691 patients. We confirmed that single-agent bortezomib or bortezomib-based regimens as consolidation therapy markedly improved PFS. However, this did not translate into an evident benefit, as OS was not significantly improved. Notably, there were higher rates of CR/nCR after single-agent bortezomib or bortezomib-based regimens as consolidation therapy. Similarly, consideration therapy achieved a superior rate of at least VGPR.

We planned to extract data on toxicity to evaluate the safety of single-agent bortezomib or bortezomib-based regimens as consolidation therapy. However, only the incidence of peripheral neuropathy was reported in both trials. Our results show that consolidation therapy increased the risk of peripheral neuropathy. The higher risk of peripheral neuropathy greater than (>) grade 2 was also seen. Therefore, peripheral neuropathy should be carefully monitored.

There are a number of limitations of our meta-analysis. The most obvious limitation was that only two studies met the inclusion criteria. Our work was also only based on the aggregate study, not on analysis of individual patient data, and is therefore limited in time-to-event analyses. Nevertheless, the several strengths of our meta-analysis outweigh the limitations. First, the quality of a meta-analysis is always subject to the quality of the included studies and the studies used in our meta-analysis were both of high quality. Both trials were large RCTs that reported double blinding of the participants and outcome assessors and described power analyses. Second, the efficacy and safety outcomes were defined similarly in both the indi-

vidual trials included in our meta-analysis. Furthermore, to our knowledge, this meta-analysis was the first systematic review to evaluate specifically the efficacy and safety of single-agent bortezomib or bortezomib-based regimens as consolidation therapy after ASCT in patients with MM.

In conclusion, we showed that single-agent bortezomib or bortezomib-based regimens as consolidation therapy for patients with MM after ASCT improved PFS and response rate. However, peripheral neuropathy must be closely monitored and longer follow-up and additional high quality RCTs are needed to evaluate the effects of consolidation therapy on OS.

Acknowledgements

This study was supported by Grants from the National Natural Science Foundation of China (No. 81372391, 81071856 and 81228016), Shanghai Science and Technology Program (No. 12410705100), and Shanghai Tenth People's Hospital Funds (No. 040113015). We thank Van S. Tompkins (Hampton-Dumont High School, Hampton, Iowa) for his assistance with writing.

Disclosure of conflict of interest

None.

Address correspondence to: Drs. Xiaosong Wu and Jumei Shi, Department of Hematology, Shanghai Tenth People's Hospital, Tongji University School of Medicine, 301 Yanchang Road, Shanghai 200-072, China. Tel: +86-21-66306764; Fax: +86-21-66301362; E-mail: wux163@163.com (XSW); shijumei@hotmail.com (JMS)

References

- [1] Moreau P, Avet-Loiseau H, Harousseau JL and Attal M. Current trends in autologous stem-cell transplantation for myeloma in the era of novel therapies. *J Clin Oncol* 2011; 29: 1898-1906.
- [2] Attal M, Harousseau JL, Stoppa AM, Sotto JJ, Fuzibet JG, Rossi JF, Casassus P, Maisonneuve H, Facon T, Lfrah N, Payen C and Bataille R. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. Intergroupe Francais du Myelome. *N Engl J Med* 1996; 335: 91-97.
- [3] Child JA, Morgan GJ, Davies FE, Owen RG, Bell SE, Hawkins K, Brown J, Drayson MT and Selby PJ. High-dose chemotherapy with hematopoi-

Bortezomib therapy for myeloma

- etic stem-cell rescue for multiple myeloma. *N Engl J Med* 2003; 348: 1875-1883.
- [4] Lenhoff S, Hjorth M, Holmberg E, Turesson I, Westin J, Nielsen JL, Wisloff F, Brinch L, Carlson K, Carlsson M, Dahl IM, Gimsing P, Hippe E, Johnsen HE, Lamvik J, Lofvenberg E, Nesthus I and Rodger S. Impact on survival of high-dose therapy with autologous stem cell support in patients younger than 60 years with newly diagnosed multiple myeloma: a population-based study. *Nordic Myeloma Study Group. Blood* 2000; 95: 7-11.
- [5] Harousseau JL, Attal M, Avet-Loiseau H, Marit G, Caillet D, Mohty M, Lenain P, Hulin C, Facon T, Casassus P, Michallet M, Maisonneuve H, Benboubker L, Maloisel F, Petillon MO, Webb I, Mathiot C and Moreau P. Bortezomib plus dexamethasone is superior to vincristine plus doxorubicin plus dexamethasone as induction treatment prior to autologous stem-cell transplantation in newly diagnosed multiple myeloma: results of the IFM 2005-01 phase III trial. *J Clin Oncol* 2010; 28: 4621-4629.
- [6] Cavo M, Tacchetti P, Patriarca F, Petrucci MT, Pantani L, Galli M, Di Raimondo F, Crippa C, Zamagni E, Palumbo A, Offidani M, Corradini P, Narni F, Spadano A, Pescosta N, Deliliers GL, Ledda A, Cellini C, Caravita T, Tosi P and Baccarani M. Bortezomib with thalidomide plus dexamethasone compared with thalidomide plus dexamethasone as induction therapy before, and consolidation therapy after, double autologous stem-cell transplantation in newly diagnosed multiple myeloma: a randomised phase 3 study. *Lancet* 2010; 376: 2075-2085.
- [7] Sonneveld P, Goldschmidt H, Rosinol L, Blade J, Lahuerta JJ, Cavo M, Tacchetti P, Zamagni E, Attal M, Lokhorst HM, Desai A, Cakana A, Liu K, van de Velde H, Esseltine DL and Moreau P. Bortezomib-based versus nonbortezomib-based induction treatment before autologous stem-cell transplantation in patients with previously untreated multiple myeloma: a meta-analysis of phase III randomized, controlled trials. *J Clin Oncol* 2013; 31: 3279-3287.
- [8] Nooka AK, Kaufman JL, Behera M, Langston A, Waller EK, Flowers CR, Gleason C, Boise LH and Lonial S. Bortezomib-containing induction regimens in transplant-eligible myeloma patients: a meta-analysis of phase 3 randomized clinical trials. *Cancer* 2013; 119: 4119-4128.
- [9] Cavo M, Rajkumar SV, Palumbo A, Moreau P, Orłowski R, Blade J, Sezer O, Ludwig H, Dimopoulos MA, Attal M, Sonneveld P, Boccadoro M, Anderson KC, Richardson PG, Bensinger W, Johnsen HE, Kroeger N, Gahrton G, Bergsagel PL, Vesole DH, Einsele H, Jagannath S, Niesvizky R, Durie BG, San MJ and Lonial S. International Myeloma Working Group consensus approach to the treatment of multiple myeloma patients who are candidates for autologous stem cell transplantation. *Blood* 2011; 117: 6063-6073.
- [10] Ludwig H, Durie BG, McCarthy P, Palumbo A, San MJ, Barlogie B, Morgan G, Sonneveld P, Spencer A, Andersen KC, Facon T, Stewart KA, Einsele H, Mateos MV, Wijermans P, Waage A, Beksac M, Richardson PG, Hulin C, Niesvizky R, Lokhorst H, Landgren O, Bergsagel PL, Orłowski R, Hinke A, Cavo M and Attal M. IMWG consensus on maintenance therapy in multiple myeloma. *Blood* 2012; 119: 3003-3015.
- [11] Cavo M, Brioli A, Tacchetti P, Zannetti BA, Mancuso K and Zamagni E. Role of consolidation therapy in transplant eligible multiple myeloma patients. *Semin Oncol* 2013; 40: 610-617.
- [12] Cavo M, Pantani L, Petrucci MT, Patriarca F, Zamagni E, Donnarumma D, Crippa C, Boccadoro M, Perrone G, Falcone A, Nozzoli C, Zambello R, Masini L, Furlan A, Brioli A, Derudas D, Ballanti S, Dessanti ML, De Stefano V, Carella AM, Marcatti M, Nozza A, Ferrara F, Callea V, Califano C, Pezzi A, Baraldi A, Grasso M, Musto P and Palumbo 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.
- [13] Mellqvist UH, Gimsing P, Hjertner O, Lenhoff S, Laane E, Remes K, Steingrimsdottir H, Abildgaard N, Ahlberg L, Blimark C, Dahl IM, Forsberg K, Gedde-Dahl T, Gregersen H, Gruber A, Guldbrandsen N, Haukas E, Carlson K, Kvam AK, Nahi H, Lindas R, Andersen NF, Turesson I, Waage A and Westin J. Bortezomib consolidation after autologous stem cell transplantation in multiple myeloma: a Nordic Myeloma Study Group randomized phase 3 trial. *Blood* 2013; 121: 4647-4654.
- [14] Belch A, Shelley W, Bergsagel D, Wilson K, Klimo P, White D and Willan A. A randomized trial of maintenance versus no maintenance melphalan and prednisone in responding multiple myeloma patients. *Br J Cancer* 1988; 57: 94-99.
- [15] Berenson JR, Crowley JJ, Grogan TM, Zangmeister J, Briggs AD, Mills GM, Barlogie B and Salmon SE. Maintenance therapy with alternate-day prednisone improves survival in multiple myeloma patients. *Blood* 2002; 99: 3163-3168.
- [16] Shustik C, Belch A, Robinson S, Rubin SH, Dolan SP, Kovacs MJ, Grewal KS, Walde D, Barr R, Wilson J, Gill K, Vickars L, Rudinskis L,

Bortezomib therapy for myeloma

- Sicheri DA, Wilson K, Djurfeldt M, Shepherd LE, Ding K and Meyer RM. A randomised comparison of melphalan with prednisone or dexamethasone as induction therapy and dexamethasone or observation as maintenance therapy in multiple myeloma: NCIC CTG MY.7. *Br J Haematol* 2007; 136: 203-211.
- [17] Myeloma Trialists' Collaborative Group. Interferon as therapy for multiple myeloma: an individual patient data overview of 24 randomized trials and 4012 patients. *Br J Haematol* 2001; 113: 1020-1034.
- [18] Attal M, Harousseau JL, Leyvraz S, Doyen C, Hulin C, Benboubker L, Yakoub AI, Bourhis JH, Garderet L, Pegourie B, Dumontet C, Renaud M, Voillat L, Berthou C, Marit G, Monconduit M, Caillot D, Grobois B, Avet-Loiseau H, Moreau P and Facon T. Maintenance therapy with thalidomide improves survival in patients with multiple myeloma. *Blood* 2006; 108: 3289-3294.
- [19] Morgan GJ, Gregory WM, Davies FE, Bell SE, Szubert AJ, Brown JM, Coy NN, Cook G, Russell NH, Rudin C, Roddie H, Drayson MT, Owen RG, Ross FM, Jackson GH and Child JA. The role of maintenance thalidomide therapy in multiple myeloma: MRC Myeloma IX results and meta-analysis. *Blood* 2012; 119: 7-15.
- [20] Cavo M, Tacchetti P, Patriarca F, Petrucci MT, Pantani L, Galli M, Di Raimondo F, Crippa C, Zamagni E, Palumbo A, Offidani M, Corradini P, Narni F, Spadano A, Pescosta N, Deliliers GL, Ledda A, Cellini C, Caravita T, Tosi P and Baccarani M. Bortezomib with thalidomide plus dexamethasone compared with thalidomide plus dexamethasone as induction therapy before, and consolidation therapy after, double autologous stem-cell transplantation in newly diagnosed multiple myeloma: a randomised phase 3 study. *Lancet* 2010; 376: 2075-2085.