Once-Weekly 1.6 mg/m² Bortezomib BCD Regimen in Elderly Patients with Newly Diagnosed Multiple Myeloma Who are Unfit for Standard Dose Chemotherapy

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Abstract Bortezomib has shown anti-myeloma effects in combination with alkylating agents, but clinical benefits can be limited by neurotoxicity. There is less information on the efficacy and tolerability of once-weekly 1.6 mg/m² bortezomib combined with cyclophosphamide and dexamethasone (BCD) regimen in elderly patients with newly diagnosed multiple myeloma who are unfit for standard dose chemotherapy. Here, we report our experience of weekly 1.6 mg/m² intravenous bortezomib in this group of patients. Between March 2010 and February 2015, we treated 34 newly diagnosed elderly patients with the combination of bortezomib 1.6 mg/m² intravenously on days 1 and 8; cyclophosphamide 200 mg/m² intravenously on days 1–4; dexamethasone 20 mg intravenously on days 1–4, and 8–11. Among the 34 patients, 14 (41 %) responded with complete response (CR), 6 (18 %) with very good partial response (VGPR) and 10 (29 %) with partial response (PR). The overall response rates were 88 %. After 2 cycles of treatments, the survival of patients who attained a response of VGPR or CR was significantly longer than those with PR or resistance to BCD, for both progression-free survival (PFS) (21.4 vs. 10.6 months, $p = 0.002$) and overall survival (OS) (23.0 vs. 16.8 months, $p = 0.043$). The 2-year PFS and OS were 26.5 and 64.7 % respectively in

these elderly multiple myeloma patients in our study. Grade 1/2 neuropathy was observed in 20 % of the cycles while grade 3/4 neuropathy was not observed. No patients withdrew due to neuropathy or other side effects. Once-weekly bortezomib at 1.6 mg/m² BCD regimen is both effective and safe in elderly patients with newly diagnosed multiple myeloma who are unfit for standard dose chemotherapy.

Keywords Multiple myeloma · Bortezomib · Cyclophosphamide · Elderly · Toxicity

Introduction

Multiple myeloma (MM) is a neoplastic plasma-cell disorder characterized by clonal proliferation of malignant plasma cells in the bone marrow microenvironment, monoclonal protein in the blood or urine, and associated organ dysfunction [1]. With the introduction of autologous stem-cell transplantation (ASCT), new immunomodulatory drugs (IMiDs) such as thalidomide and lenalidomide, and the proteasome inhibitor bortezomib, management of myeloma and survival have changed dramatically in the last decades [2–5].

However, MM is a disease of older adults. Median age at diagnosis is 70 years. Even in Asia, the median age of all patients is 62 years [6]. Most studies suggest that improvements in older adults with MM have not been as great as that in younger individuals [7–9]. Patients older than 65 years of age are generally considered ineligible for high-dose therapy (HDT) followed by ASCT [1]. But elderly patients with myeloma are heterogeneous. Physical and cognitive functions can be highly variable among adults of the same age. So the operative cutoff age of

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65 years is not sufficient to identify elderly patients. To those fit patients, full-dose, triple therapies or even more intensive approach could be well tolerated [10, 11], while the unfit patients with MM are particularly vulnerable to adverse events (AEs) associated with multidrug combinations, which can lead to dose reductions or cessation of therapy altogether. Unfit patients are characterized by older age, frailty, disability and comorbidity [12]. These unfit patients usually need gentler approaches taking into account age, physical condition (cardiac, pulmonary, hepatic, gastrointestinal, renal), and comorbidity status. It is critical that efficacy must be balanced against risk of toxicity of therapy, and emphasis is given to maintaining good quality of life in unfit older adults with MM [8]. Treatment discontinuation due to therapy-related adverse events is an important factor that negatively impacts outcome [13]. Indeed, interruption translates into dose-reduction and reduced cumulative dose-intensity, affecting efficacy of therapy.

Bortezomib is an important option for initial therapy in older adults with MM. Either intravenously or subcutaneously, bortezomib induces high and rapid responses, without the risk of thromboembolism and may be used in patients with renal failure. Significant obstacles for the timely delivery of bortezomib are peripheral neuropathy and thrombocytopenia, which can be reduced by subcutaneous or once per week administration [14, 15]. When the twice-per-week bortezomib schedule was decreased to once per week, the rate of grade 3–4 peripheral neuropathy was significantly reduced from 28 to 8 %, without affecting efficacy [16]. VMP (Velcade, melphalan and prednisone) today is considered one of the standard approaches for elderly MM patients, and the once-weekly bortezomib schedule is a valid alternative strategy [17]. Bortezomib was also evaluated in combination with cyclophosphamide and dexamethasone (BCD) in newly diagnosed MM patients, both eligible and ineligible for ASCT [18]. Nevertheless, BCD regimens were inevitably associated with increased toxicity, resulting in a transient decrease in the global health score [19].

Since bortezomib is generally well tolerated at doses up to 1.6 mg/m^2 on a once-weekly schedule [16], we hypothesized that this dose of once-weekly bortezomib plus cyclophosphamide and dexamethasone (BCD) is as effective as the standard BCD, resulting in less toxicity and avoiding bortezomib treatment discontinuation, which eventually leads to decreased efficacy. The aim of this study is to evaluate the antitumor efficacy and safety profile of the BCD regimen as a frontline induction therapy in elderly patients with newly diagnosed MM, who were unfit for standard dose chemotherapy.

Methods

Patients

Our study involved elderly patients with newly diagnosed, symptomatic MM and measurable disease who had not received prior therapy. All patients met the International Myeloma Working Group (IMWG) MM diagnostic criteria [20] and was staged using the Durie-Salmon (DS) staging system and the International Staging System (ISS) [21]. Inclusion criteria also included the following (1) age ≥ 65 years; (2) frailty (meet at least three conditions: weakness, poor endurance, weight loss, low physical activity, and slow gait speed) or comorbidity (concurrent presence of at least 2 chronic diseases) or disability (difficulty or dependency in carrying out activities of daily living) and unfit for standard dose chemotherapy [12]; (3) Eastern Cooperative Oncology Group performance status of <3 ; (4) aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase not higher than three times the upper limit of the normal value; (5) serum total bilirubin concentration not higher than two times the upper limit of the normal value; (6) absolute neutrophil count (ANC) $>1000/\mu\text{L}$, hemoglobin level $>10 \text{ g/dL}$ and platelets $>80,000/\mu\text{L}$.

Exclusion criteria included (1) significant pre-existing peripheral neuropathy (defined as $\geq$ grade 3); (2) left ventricular ejection fraction ≤ 0.50 , or those who had symptoms of congestive heart failure; (3) uncontrolled angina, or significant arrhythmias; (4) recurrent deep vein thrombosis or pulmonary thromboembolism; (5) chemotherapeutic drug allergy, for example, patients with hypersensitivity to bortezomib.

Study design

This was a single arm, prospective, single-center study, conducted from March 2010 to February 2015. All patients signed informed consent that addressed all potential side effects. The study was approved by the Hospital Ethics Committee and conducted in accordance with the Declaration of Helsinki. The primary objective was to determine the overall response rate (ORR) which was classified as complete response (CR), very good partial response (VGPR), or partial response (PR) to the once-weekly BCD regimens. Secondary objectives included time to response, time to progression-free survival (PFS), overall survival (OS), and adverse drug events. PFS was defined as the time to progression or death from any cause during treatment with BCD. OS was measured from treatment until death from any cause.

Patients received four cycles of BCD consisting of bortezomib 1.6 mg/m² intravenously on days 1 and 8; cyclophosphamide 200 mg/m² intravenously on days 1–4; dexamethasone 20 mg intravenously on days 1–4, and 8–11, as a 3 weekly cycle. BCD was based on a combination of known efficacy and toxicity data of proteasomes inhibitor and cytotoxic agents in multiple myeloma. From the experience of treating myeloma with bortezomib–cyclophosphamide–dexamethasone combination regimen, cyclophosphamide administered daily at 200 mg/m² on days 1–4 every 3 weeks translates into a comparable accumulated dosage of cyclophosphamide in comparison with weekly pulsed high-dose of cyclophosphamide. Considering that the target population of this study was elderly patients who were unfit for standard dose chemotherapy, the regimen schedule planned at consecutive 4 days of low-dose cyclophosphamide was more feasible or tolerable than weekly pulses.

Evaluation of patients was carried out after every 2 cycles of treatment. After four cycles, four additional cycles were given unless there was tumor progression or unacceptable side effects. If the patients achieve more than PR after eight cycles of chemotherapy, they received thalidomide as maintenance, at a dose of 50–100 mg per night. Patients were removed from the study once the disease progressed at any time.

All patients received a proton pump inhibitor prophylactically and monthly bisphosphonates treatment if they had bony involvement. Blood transfusion and other supportive care were provided when indicated. Routine prophylaxis included acyclovir for zoster and Co-trimoxazole for *Pneumocystis carinii* prevention.

Dose modification and treatment delay

The start of a new cycle could be delayed on a weekly basis (for a maximum of 3 weeks) until recovery from toxicity (to a grade 2 or less). Bortezomib was withheld for grade 4 hematological toxicities and grade 3 or more non-hematological toxicities. After adverse events had resolved, bortezomib dose was reduced from 1.6 to 1.3 mg/m². If the patient had peripheral neuropathy of grade 2 or 1 with pain, bortezomib was reduced to 1.3 mg/m²; for grade 3 or more peripheral neuropathy, bortezomib was withheld until the peripheral neuropathy resolved to baseline and then restarted at 1.0 mg/m². In the maintenance phase, thalidomide was omitted until the toxicity resolved to baseline or decreased to grade 1. Thalidomide was discontinued permanently in the event of thrombosis.

Assessments

Response was assessed according to the criteria of The European Group for Blood and Bone Marrow Transplant

[20]. CR required negative immunofixation of myeloma protein in serum and urine with less than 5 % plasma cells in bone marrow; VGPR required ≥ 90 % or greater reduction in serum M-component plus urine M-component < 100 mg per 24 h; PR required ≥ 50 % reduction of serum M protein and/or reduction of Bence Jones protein by ≥ 90 %, maintained for at least 3 months. Progressive disease (PD) was defined as an increase by greater than 25 % of serum or urine M-component.

Adverse drug events were monitored and graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (v4.0, 2009) at each visit after the end of the chemotherapy and every two months during maintenance.

Statistical methods

Descriptive statistics, including median and range, were used to summarize continuous variables. Objective response rate was performed on an intention-to-treat analysis and on patients who completed every two cycles. OS, PFS and analysis for toxicity was performed on all patients who received the study drug. Statistical analyses were performed with SPSS 13.0 statistical software. OS and PFS were analyzed using Kaplan–Meier survival curve estimates. A *p* value < 0.05 was considered statistically significant.

Results

Patient characteristics

Between March 2010 and February 2013, a total of 55 elderly patients with newly diagnosed MM were offered this study. Three patients refused to participate and opted for other methods of treatment. Ten patients did not meet any of the following conditions: frailty, comorbidity or disability. Another 8 patients did not meet the other eligibility criteria or had one or more exclusion criteria. Consequently, a total of 34 patients were enrolled into the study. Basic information and disease characteristics of the 34 patients are shown in Table 1.

The median age was 69 years (range 65–81) and 41.2 % of patients were older than 70 years. In terms of immunoglobulin classes, IgG and IgA were the majority types in all patients (94.1 %). Among the evaluable patients, 85.3 % had Durie–Salmon (DS) Stage III disease, while 91.2 % had International Staging System (ISS) stage II or III disease.

The most common frailty was poor endurance and low physical activity. As for comorbidity, hypertension, coronary heart disease and diabetes accounted for the majority.

Table 1 Patient baseline characteristics

Characteristic	No. of patients (n = 34)	%
Median age, years (range)	69	(65–81)
Age		
≤70-year old	20	58.8
>70-year old	14	41.2
Male sex	20	58.8
Myeloma type		
IgG	17	50.0
IgA	15	44.1
Light chain	2	5.9
Durie–Salmon stage		
I	2	5.9
II	3	8.8
III	29	85.3
Serum creatinine >2 mg/dL	3	8.8
International Staging System stage		
I	3	8.8
II	17	50.0
III	14	41.2
ECOG		
0	8	23.5
1	12	35.3
2	14	41.2
Reason for classifying as “unfit”		
Frailty	11	32.4
Comorbidity	18	52.9
Disability	5	14.7
Median bone marrow plasma cell, % (range)	30	(7–90)
Calcium >12 mg/dL	23	67.6
Bone disease present, % (skeletal abnormality)	28	82.4
Cytogenetic risk stratification		
Standard risk	24	70.6
High risk ^a	3	8.8
Not performed/Available	7	20.6

Values are presented as number (%)

^a Hypodiploidy, del 13, del 17p, t(4;14), t(14;16) or 1q amplification by standard cytogenetics or fluorescence in situ hybridization (FISH)

Five patients needed assistance for activities of daily living, which meet the definition of disability. The average number of plasma cells in the bone marrow was 30 % (range 7–90 %). There were 67.6 % of patients with an elevated serum calcium. The vast majority (82.4 %) of patients had presence of bone disease. High-risk MM was present in 3 patients based on the presence of hypodiploidy, del 13, del 17p, t(4;14), t(14;16) or 1q amplification by standard cytogenetics or fluorescence in situ hybridization

(FISH). Twenty-four patients belonged to standard chromosome risk group, and the remaining patients had no cytogenetic data available.

Treatment response

The median number of treatment cycles were 8 cycles (range 1–8), and the number of cycles delivered were 202. Among 34 patients, 14 patients (41 %) responded with CR, 6 patients (18 %) with VGPR and 10 (29 %) with PR as their best responses respectively, which were presented in Fig. 1. The ORRs [$\geq$ partial response (PR)] were 88 %. The median time to PR was after 2 cycles of treatment (2–4 cycles). The cumulative best response rates were presented in Fig. 2 according to the number of treatment cycles. The median time to achieve best response was after 4 cycles of treatment (2–6 cycles). The median remission time for all patients with responsive disease was 15 months, with 8 patients remained in CR, 1 patient remained in VGPR and 4 patients remained in PR. Eleven patients had disease progression during chemotherapy, and 10 patients had disease recurrence or progression during maintenance phase.

We further analysed the characteristics of the 4 patients who had disease progression after two courses of BCD regimen. Table 2 is the clinical data of these 4 patients. Two patients who were very old and with comorbidities (hypertension and diabetes) rapidly deteriorated and demised due to disease progression. The other two patients were salvaged with DTPACE chemotherapy and obtained a longer OS. Analysing for common features in these four patients, their light chains were all kappa chain and all of them had extramedullary involvement, which seems to predict poor response to the BCD regimen. However, due to small number of cases, this was not statistically significant.

Survival

During the 2-year follow-up period, 12 patients have died and another 9 patients experienced disease progression. The remaining 13 patients remained in remission. The median PFS were 13.9 months and the median OS was 20.1 months. The survival of patients who attained VGPR or CR after 2 cycles of treatment was significantly longer than those with PR or resistance to BCD, for both the PFS (21.4 vs. 10.6 months, $p = 0.002$) and OS (23.0 vs. 16.8 months, $p = 0.043$) (Fig. 3). The corresponding 2-year PFS and OS was 26.5 % and 64.7 % respectively in our study cohort of elderly MM patients.

There was no significant difference in ORR between patients with different ISS or DS staging and immunoglobulin classes. However, outcome for patients

Fig. 1 Best response during treatment. *CR* complete response, *VGPR* very good partial response, *PR* partial response, *SD* stable disease, *PD* progressive disease

Fig. 2 Cumulative best response by treatment cycles. *CR* complete response, *VGPR* very good partial response, *PR* partial response, *SD* stable disease, *PD* progressive disease

between 65 and 70 year old was better than patients beyond 70 year old, both in PFS (20.3 vs. 14.2 months, $p = 0.030$) and OS (22.5 vs. 16.6 months, $p = 0.022$).

Treatment-related toxicity

In total, 202 cycles of BCD therapy were delivered. The weekly regimen at 1.6 mg/m² of bortezomib in BCD was well tolerated. Table 3 shows the frequency of common side effects (hematologic and non-hematologic toxicities).

Grade 3/4 neuropathy was not observed while grade 1/2 neuropathy was observed in 20 % of the chemotherapy cycles. No patients withdrew due to neuropathy or other side effects.

The most common grade 1/2 adverse events were hematologic toxicity, including leukopenia, anemia and thrombocytopenia. The most common grade 1/2 non-hematologic toxicities included vomiting (26 %), peripheral neuropathy (20 %), diarrhea (18 %) and constipation (9 %). We did not find any subset of patients with greater propensity to develop cytopenia, which occurred randomly in patients with various ages, stages, ECOG status and tumour load. However, patients with chronic diseases (such as diabetes) seemed to be more prone to develop non-hematologic toxicities such as infections and peripheral neuropathy, which were all reversible. Infectious complications were the most significant grade 3/4 toxicities (14 %), most of them were pneumonia. Of the four patients who died during the period of chemotherapy, none was considered as related to treatment. The causes of their death were all due to disease progression, resulting in suppression of normal hematopoietic function and various complications. In all treatment cycles, 24 cycles (11.9 %) and 12 patients (35.3 %) were delayed, and needed dose modifications. The main reason was hematologic toxicity (including neutropenia and thrombocytopenia), which together accounted for 91.7 %, followed by herpes zoster (8.3 %).

Discussion

The number of older adults diagnosed with MM will increase by nearly 80 % in the next two decades, but the improvements in older adults have not been as great as those in younger adults with MM over the last 20 years [8]. The unfit older adults often have other chronic health problems and are likely to be receiving multiple medications that may influence their MM treatment plan [22]. Frailty, comorbidity, and disability all occur commonly among elderly patients. Given that more and more unfit elderly patients will face adverse drug reactions and the association of AEs with treatment discontinuation, the

Table 2 Clinical profile of non-responders

Age	Gender	Myeloma type	DS stage	ISS stage	ECOG	Unfit reason	Median bone marrow plasma cell	Extramedullary disease	Cytogenetic risk stratification	OS
80	Male	IgG,kappa	IIIA	III	2	Comorbidity	52 %	Yes	1q amplification	3 months
81	Female	IgA,kappa	IIIB	III	2	Comorbidity	90 %	Yes	Standard risk	1 months
68	Female	IgG,kappa	IIIA	II	0	Disability	14.50 %	Yes	t(4;14)	24 months
66	Male	IgG,kappa	IIIA	II	2	Frailty	30 %	Yes	Standard risk	15 months

Fig. 3 PFS and OS of all patients. *Left panel* longer PFS in CR and VGPR patients after 2 courses of BCD compared with PR, SD and PD patients (21.4 vs. 10.6 months, $p = 0.002$). *Right panel* longer OS in CR and VGPR patients after 2 courses of BCD compared with PR, SD and PD patients (23.0 vs. 16.8 months, $p = 0.043$)

Table 3 Toxicity of once-weekly BCD in 202 evaluable treatment cycles

	NCICTCAE 4.0 toxicity			
	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)
Hematologic				
Anemia	71 (35.14)	25 (12.38)	13 (6.43)	4 (1.98)
Neutropenia	54 (26.73)	25 (12.38)	14 (6.93)	8 (3.96)
Thrombocytopenia	57 (28.21)	16 (7.92)	4 (1.98)	2 (0.99)
Non-hematologic				
Vomiting	49 (24.26)	4 (1.98)	0 (0.00)	0 (0.00)
Infection	2 (0.99)	11 (5.44)	26 (12.87)	2 (0.99)
Febrile neutropenia	0 (0.00)	0 (0.00)	4 (1.98)	2 (0.99)
Constipation	17 (8.42)	2 (0.99)	2 (0.99)	0 (0.00)
Diarrhea	25 (12.38)	13 (6.43)	2 (0.99)	0 (0.00)
Allergy	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Rash	17 (8.42)	0 (0.00)	0 (0.00)	0 (0.00)
Peripheral neuropathy	35 (17.33)	6 (2.97)	0 (0.00)	0 (0.00)

Table shows number of cycles affected and percentage of total cycles in which the respective toxicity occurred

BCD bortezomib, cyclophosphamide and dexamethasone, NCICTCAE National Cancer Institute's Common Terminology Criteria for Adverse Events

selection of optimal therapeutic agents and dose is imperative to ensure best outcomes in older adults with MM.

Proteasome inhibitor is an important option in MM treatment regimens, although the optimal way of incorporating it is still being elucidated. In the elderly unfit MM patients, a less intensive approach should be considered, especially in the presence of neuropathy, which can adversely affect quality of life. It was demonstrated that dosing bortezomib once a week in elderly patients with relapsed/refractory MM could result in lower toxicity without impairing its effectiveness. There was also the need to modify the treatment to make bortezomib treatment more effective in older patients [23].

We performed this study to explore how treatment could be optimized for the elderly MM patients who were unfit for standard dose chemotherapy. This is the first prospective study to report the results of a modified scheme of BCD, which reduces the frequency of use of bortezomib to

once a week, but with an increased dose to 1.6 mg/m², in newly-diagnosed elderly patients with MM who are unfit for standard dose chemotherapy. There have been some literatures reporting the experience of weekly bortezomib, but they were mainly used in Caucasians, while our research focused on Chinese patients.

Several studies have reported encouraging results for MM patients with BCD regimen [19, 24–26], in both newly diagnosed and relapsed/refractory patients, including patients of all ages. The ORR ranged from 69 to 96 %. In an open-label prospective assessment, 175 patients (age 65–89 years) received BCD induction therapy. Bortezomib was administered at 1.3 mg/m² intravenously on days 1, 4, 8, and 11 every 3 weekly for 4 cycles. ORR after the induction chemotherapy was 69.7 %. PFS and OS at 5 years reached 58.2 and 79.9 % respectively. There were 13 deaths out of the 175 patients (7.4 %) in the BCD group. In another randomized, multicenter, phase 2 study, patients

received bortezomib 1.3 mg/m^2 (days 1, 4, 8, 11) in 3-weekly cycles (maximum 8 cycles). Response of VGPR or better was seen in 41 % (CR rate of 22 %) of patients, with a corresponding 1-year PFS of 93 %. In our study with elderly unfit patients, ORR (88 %) ($\geq$ VGPR rate of 59 %) is comparable to these results with a twice-weekly regimen, but the PFS and OS results are lower. This is likely because our patient population in this study was at high risk with a median age of 69 years, and had pre-existing frailty, comorbidity, or disability. In comparison, some of the mentioned studies were not limited to the elderly, and in addition incorporated bortezomib for maintenance therapy. It is possible that if we use bortezomib which is more potent than thalidomide as maintenance therapy, our PFS and OS may improve significantly.

VMP (Velcade, Melphalan and Prednisolone) is considered one of the standard approaches for elderly MM patients. A large-scale randomized clinical trial published in 2010 compared the effects with VMP and VTP (bortezomib plus thalidomide and prednisone), in which bortezomib was also used once a week [17]. 80 % patients in the VMP group and 81 % in the VTP group achieved PR or better, including 20 and 28 % CR. But VTP regimen resulted in more serious adverse events (31 %) and discontinuations (17 %). The occurrence rate of peripheral neuropathy was 7 % in the VMP group and 9 % in the VTP group respectively. The 3-year OS for patients was 70 %. In our study, both ORR and CR are better, and no grade 3/4 peripheral neuropathy was observed among all patients. But the survival in our study is lower compared to VMP or VTP. The possible reason is that the total dose of bortezomib in our study was nearly 1/3 less than VMP or VTP in the period of induction therapy, and there was no bortezomib for maintenance therapy in our study.

In terms of response duration, it was not surprising that good responders (CR and VGPR) had significantly longer OS and PFS than patients in PR and non-responders. An analysis performed on 4990 MM patients treated with conventional chemotherapy and ASCT showed that patients achieving CR after induction had significantly longer PFS and OS compared to those who obtained a PR only (59–89 vs. 39–68 months) [27]. The depth of response and its duration are important prognostic factors in MM. Attaining a CR proved to be an independent predictor of longer survival in elderly patients treated with both conventional chemotherapy and novel agents [28, 29]. Our study also confirms this conclusion. Achievement of VGPR or CR after 2–4 cycles predicts significantly prolonged PFS and OS. This was statistically significant for PFS. Therefore, we believe that in addition to CR, patients who could achieve VGPR also have a good prognosis.

Furthermore, we found that after two cycles, only 2 patients achieved CR while 16 patients were in VGPR.

After 4 cycles of chemotherapy, 8 of the original 16 VGPR patient could achieve CR. A further 2 cycles resulted in 2 more patients achieving CR, but by 8 cycles, there was no further CR from the patients who remained in VGPR. Therefore, we believe that the response achieved after four cycles could be considered the best outcome a patient can possibly achieved. Thus, if the patient could only reach PR after 4 cycles or VGPR after 6 cycles, there is no benefit in persisting with further cycles.

Another important issue in the treatment of elderly patients is toxicity profile of the regimen. Unfit patients are more susceptible to AEs with subsequent treatment discontinuations that significantly affect dose-intensity and efficacy. Occurrence of serious adverse events during treatment should be carefully taken into account to adjust doses and optimize outcomes. Bortezomib-induced peripheral neuropathy is a common dose-limiting toxicity. In patients with newly diagnosed MM receiving twice-weekly bortezomib, it has been reported that 9–18 % of patients developed grade 3 neuropathy. However, recent data indicate that a once-weekly schedule of bortezomib [30] or administration via subcutaneous injection [31] result in significantly lower rates of peripheral neuropathy compared with standard twice-weekly IV dosing.

In this study, we have also shown that the once-weekly BCD regimen had a favorable toxicity profile, even with bortezomib dose increased to 1.6 mg/m^2 per dose. We did not observe any grade 3/4 neuropathy, and grade 1/2 neuropathy occurred in only 20 % of the cycles. It means that 80 % of the cycles were not affected by neuropathy in the course of treatment. Other toxicities during therapy were mild. Although 11.9 % of the cycles (35.3 % patients) experienced chemotherapy delays due to bone marrow suppression, no patients discontinued chemotherapy treatment due to side effects. Dose-escalation of bortezomib, even in three-drug combinations is safe in a younger population [32]. Our results show that higher dose of bortezomib at 1.6 mg/m^2 , more commonly used in treatment of lymphoma, is also a safe starting dose in new diagnosed elderly MM patients unfit for standard dose chemotherapy.

Some limitations of this study should be discussed. Firstly, this is not a randomized controlled study. All efficacy and side effects data were compared to the twice a week BCD program reported in the literature. If a randomized controlled study could be performed in the future, the results obtained may be more meaningful. Secondly, it is now known that subcutaneous bortezomib reduces incidence of peripheral neuropathy, but such data was not available when we started the study. In future we should use subcutaneous bortezomib for clinical trials, which could help to find the best way of using bortezomib. Thirdly, the number of cases we have was

not large and the observation time was not long. Our result must be confirmed in future larger studies with a longer follow up.

In summary, based on these encouraging results of BCD regimen with once-weekly bortezomib at 1.6 mg/m², we conclude that this new induction strategy might be both effective and safe in elderly patients with newly diagnosed MM who are unfit for standard dose chemotherapy. The efficacy is comparable to other twice-weekly BCD regimen but with significantly reduced side effects.

The study was approved by the Hospital Ethics Committee and conducted in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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Compliance with ethical standards

Conflict of interest All authors have no conflicts of interest.

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