



Treatment outcome and prognostic factor in fit elderly patients with multiple myeloma received frontline induction of bortezomib based regimen (PAD or VCD)

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Background: Few clinical trials have head to head compared bortezomib, doxorubicin and dexamethasone (PAD) and bortezomib, cyclophosphamide and dexamethasone (VCD) regimen in multiple myeloma (MM), especially for the elderly patients.

Methods: In this study, we included 64 fit patients who were treated with frontline induction of PAD or PCD. The effect of the bortezomib triple regimens and prognostic factors were evaluated.

Results: Among the 64 patients, 20 (31.25%) were with international stage III disease. The median age was 67 years [65–75]. After completion of induction therapy, the overall response rate (ORR) 93.7%, complete remission (CR) rate was 32.8%. With a median follow up time of 28 [8–79] months, the median progressive free survival (PFS) and overall survival (OS) were 21.6 and 56.8 months respectively. There was no difference in term of CR rate, PFS, OS and adverse effects between two groups of patients induced by PAD or VCD regimens. Multivariable Cox analysis showed that low albumin (ALB) (<35 g/L) and elevate lactate dehydrogenase (LDH) (> normal) were independent prognostic factor of OS (OR=2.980, 95% CI, 1.021–8.699, P=0.025 and OR=2.715, 95% CI, 1.184–6.223, P=0.018).

Conclusions: PAD and VCD regimens showed equivalent efficacy and tolerability for fit elderly MM patients. Low ALB and high LDH were adverse prognostic factors associated with inferior OS, even in the era of novel agents.

Keywords: Multiple myeloma (MM); elderly patients; bortezomib; prognostic; adverse event

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Introduction

Multiple myeloma (MM) is an incurable hematological malignancy originating from plasma cell. With conventional chemotherapy, such as melphalan and prednisone (MP), vincristine, adriamycin and dexamethasone (VAD), the overall response rate (ORR) and complete remission (CR) rate was approximately 60% and less than 5%, respectively, with a median overall survival (OS) time of 2 to 3 years (1). Throughout the last decade, the advent of proteasome

inhibitors, such as bortezomib, lead to a revolution in MM treatment (2,3). A significantly higher CR rate (30–40%) could be achieved by using bortezomib based regimens as the frontline treatment, which could be translated to a significant improved OS (2006–2010 *vs.* 2001–2005: 5 *vs.* 3.2 years) (4–6). Hence, chemotherapy of bortezomib-based combination with two or three drugs, are recommended as standard frontline induction therapy in both transplant-eligible and -ineligible patients with MM.

Newly diagnosed MM patients aged over 65 years are generally defined as elderly MM; and not considered to be the transplant candidates. For these patients, the regimen recommended as the first line treatment (category 1) in most western guidelines included: melphalan/prednisone/bortezomib (MPB), melphalan/prednisone/thalidomide (MPT), lenalidomide/bortezomib/dexamethasone (RVD) or lenalidomide/dexamethasone (RD), on the other hand more aggressive cytotoxic agents, especially doxorubicin, which is generally suggested in younger patients, is still controversial in this group of the patients. However, due to the problem of availability of melphalan in china and registration approval of lenalidomide in frontline, we generally used bortezomib/doxorubicin/dexamethasone (PAD) or bortezomib/cyclophosphamide/dexamethasone (VCD) as the first line therapy for transplant-ineligible patients. And of note, there is no head to head study comparing PAD and VCD in elderly patients with MM.

Considering elderly patients being highly heterogeneous, the International Myeloma Working Group (IMWG) suggested the use of geriatric assessment (GA) which divides elderly patients into 3 groups: fit, intermediate-fitness, and frail. Tailored therapy was also recommended to each group (7). Precise analysis of the effects and safety of the regimens should be performed in each specific sub-group. Also, not many reports focus on the subset of the fit elderly patients with MM. Therefore, we consecutively included 64 fit elderly patients with newly diagnosed multiple myeloma (NDMM) who received PAD or VCD as induction therapy followed by a maintenance of thalidomide, to analyze its efficacy, adverse effects and prognostic factors in Chinese patients.

Methods

Patients

From May 2009 to May 2014, 64 elderly patients with NDMM aged from 65 to 75 years were included. Since we could not collect the complete data of activities of daily living (ADL) and instrumental activities of daily living (IADL) of the patients, we modified the conditions of fitness, which were defined as 'age from 65 to 75 years' and 'Charlson index [0–1]'. They received either PAD or VCD induction therapy in Ruijin Hospital Affiliated to Shanghai Jiao Tong University, School of Medicine. The study was approved by the ethic committee of Ruijin Hospital and performed according to the Declaration of Helsinki.

Informed consents were obtained from all the patients.

Evaluation of the disease and adverse events

MM was diagnosed according to standard criteria of IMWG. All the 64 patients were with symptomatic MM and measurable disease (non-secretory MM was excluded); all of them were full dose chemotherapy eligible (severe heart, lung or liver disease at baseline was excluded). The response criteria was according to the IMWG uniform response criteria for MM, including CR, very good partial response (VGPR), partial response (PR), stable disease (SD) and progressive disease (PD) (8). Adverse events were assessed and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE, version 4.0).

Treatment regimens

PAD or VCD regimen was given to the patients according to the decision of the physician. Bortezomib was administered 1.3 mg/day intravenously on days 1, 4, 8, 11 in a 28-day cycle. Doxorubicin was given 9 mg/day intravenously on days 1–4; cyclophosphamide was given 300 mg/day intravenously on days 1, 4, 8, 11; dexamethasone was administered 40 mg/day intravenously on days 1–4. All the patients received maintenance thalidomide 50–100 mg/day orally, if tolerated, continuing until disease progression. Antithrombotic agents were not routinely used. Antiviral prophylaxis (acyclovir 400 mg/day orally) has been given mandatory throughout introduction therapy since the year 2010.

Statistical analysis

Fisher's exact test was used to compare the differences in CR rates. One way Anova test was used to compare baseline characteristics in two groups. Progressive free survival (PFS) was defined as from start of treatment to disease progression, relapse, or any cause of death. OS was calculated from the diagnosis to any cause of death. Kaplan-Meier and hazard ratio analysis was used to calculate and compare the survival outcomes. Cox model was used for the multivariate analysis of associations of survival and potential prognostic factors. A limited backward selection procedure was used to exclude redundant varieties. All analyses were performed with the Statistical Software Package for the Social Sciences (SPSS version 19.0 for Windows; SPSS Inc.,

Table 1 Baseline characteristics of 64 patients

Characteristics	PAD (n=32)	VCD (n=32)	P value
Age, median [range]	67 [65–75]	67 [65–74]	0.149
Gender, male/female	25/7	18/14	0.109
M component, n [%]			0.845
IgG	15 [47]	16 [50]	
IgA	11 [34.3]	8 [25]	
IgD	2 [6.2]	3 [9.4]	
Light chain	4 [12.5]	5 [15.6]	
Hb (g/L), median [range]	95 [56–142]	79 [53–149]	0.160
PLT ($\times 10^9/L$), median [range]	174 [73–305]	167 [30–374]	0.252
LDH, median [range]	139 [64–483]	165 [69–448]	0.702
Albumin (g/L), median [range]	27 [16–38]	30 [16–42]	0.084
$\beta 2$ -MG (mg/L), median (range)	3.7 (1.7–16.1)	4.2 (1.0–17.7)	0.864
Scr ($\mu\text{mol/L}$), median [range]	84 [38–519]	90 [44–635]	0.527
DS stage, n (%)			0.709
II	5 (15.6)	3 (9.4)	
III	27 (84.4)	29 (90.6)	
ISS stage, n (%)			1.000
II	22 (68.75)	22 (68.75)	
III	10 (31.25)	10 (31.25)	

PAD, bortezomib, doxorubicin and dexamethasone; VCD, bortezomib, cyclophosphamide and dexamethasone; Hb, hemoglobin; PLT, platelet; LDH, lactate dehydrogenase; $\beta 2$ -MG, $\beta 2$ microglobulin; DS, Durie-Salmon staging system; ISS, international staging system; Scr, serum creatinine.

Chicago, IL, USA).

Results

Patients

Sixty-four patients were included, among which, 39 (61%) were male and 25 (39%) were female. The median age at diagnosis in this study was 67 years (range, 65–75 years). Of all the patients, 44 (68.75%) cases were within international staging system (ISS) stage II, 20 (30.25%) cases were within ISS stage III. There was no significant difference in patient characteristics between PAD and VCD group. The detailed baseline characteristics were listed in *Table 1*.

Treatment outcomes

Eight cycles of PAD and VCD was original scheduled for

the patients, however, a sizable portion of patients could not complete the whole regimen according to their tolerability or personal will (mostly economic reason). In both two groups, the median cycles of induction treatment were four.

After the induction therapy, the ORR/PR of all the 64 patients was 93.7% (60/64), CR rate was 32.8% (21/64). There was no significant difference between PAD and VCD group, regarding ORR (90.6% *vs.* 96.8%, respectively) and CR rate (37% *vs.* 28%, respectively) (*Table 2*).

At the time of analysis (May 31, 2016), the median follow up time was 28 months (range, 8–79 months), the median PFS and OS were 21.6 and 56.8 months for the entire group respectively (*Figure 1*).

In the PAD group, 81% (26/32) patients progressed or relapsed, and 40% (13/32) patients died. In the VCD group, 84% (27/32) patients progressed or relapsed, and 43% (14/32) patients died. There was no difference on the

Table 2 Response post PAD or VCD induction

Best response post induction	PAD (n=32) [%]	VCD (n=32) [%]	P value
CR	12 [37]	9 [28]	0.548
VGPR	6 [19]	7 [22]	
PR	11 [34]	15 [47]	
SD	3 [9]	1 [3]	

PAD, bortezomib, doxorubicin and dexamethasone; VCD, bortezomib, cyclophosphamide and dexamethasone; CR, complete response; VGPR, very good partial response; PR, partial response; SD, stable disease.

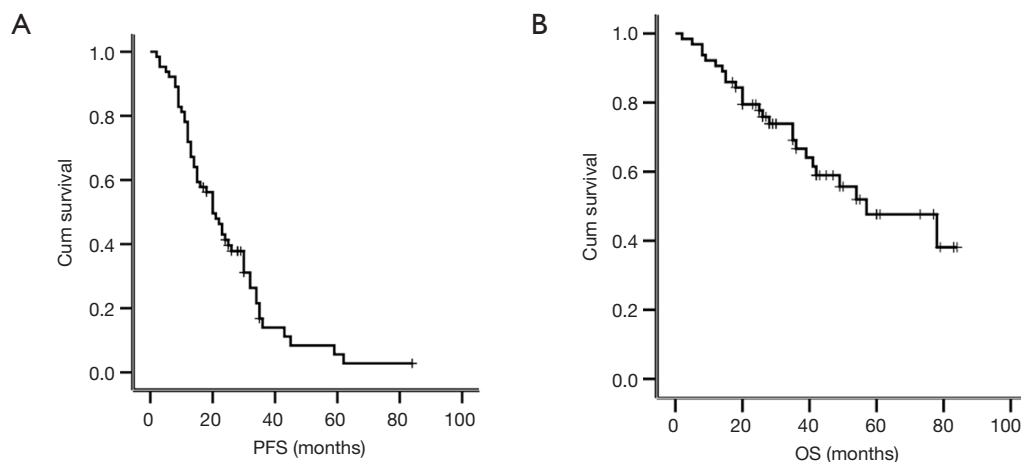


Figure 1 Survival of total 64 patients. (A) PFS; (B) OS. PFS, progressive free survival; OS, overall survival.

survival between the two groups. Two-year PFS rates were 41.4% and 40.6% for PAD and VCD group, respectively ($P=0.405$, *Figure 2A*), and five-year OS rates were 51.2% and 41.2%, respectively PAD and VCD group, respectively ($P=0.479$, *Figure 2B*).

Adverse events

Treatment related death happened in one patient in PAD group, who died from pneumonia in cycle 2. Other serious adverse events included two pneumonias and one heart failure in PAD group, and two pneumonias in VCD group.

In PAD group, the scheduled regimen was postponed in 9 patients' treatments for AE. The dose of doxorubicin was reduced to 75% in three patients, and the dose of bortezomib was reduced to 1.0 mg/m² in five patients. In VCD group, treatment was postponed in five patients for AE, the dose of bortezomib was reduced to 1.0 mg/m² in seven cases.

During the period of induction therapy, hematologic

toxicities (grade 3 to 4) included neutropenia (15.6–21.8%), anemia (15.6%) and thrombocytopenia (12.5–18.7%). The most frequent non-hematologic toxicities included infection, fatigue, constipation, diarrhea, and herpes zoster, as list in *Table 3*, cardiac toxicity was rare, which was observed in two patients (one congestive heart failure and one atrial fibrillation) in the PAD group. Peripheral neuropathy (PN) was reported in 18 (56.2%; PAD) and 20 (62.5%; VCD) patients, with 5 (15.6%; PAD) and 7 (21.8%; VCD) for grade ≥ 2 . There was no difference between the PAD group and VCD group, regarding both hematologic and non-hematologic toxicities (*Table 3*).

Prognostic analysis

In the univariate Cox analysis, we included several parameters as potential prognostic factors, such as gender, lactate dehydrogenase (LDH), albumin (ALB), ISS, Durie-Salmon (DS), CR, and serum $\beta 2$ microglobulin ($\beta 2$ -m). It was proved that only LDH level (elevated *vs.* normal)

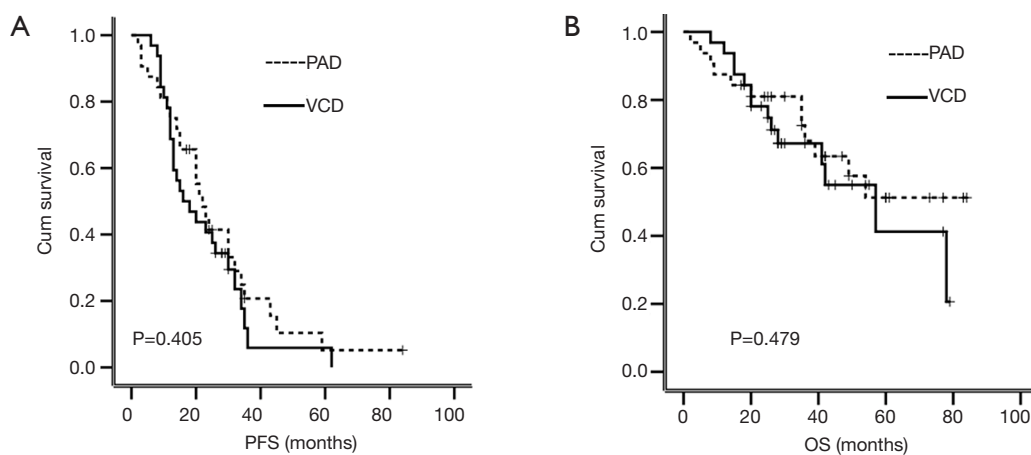


Figure 2 No difference between PAD group and VCD group in term of PFS and OS. (A) PFS; (B) OS. PAD, bortezomib, doxorubicin and dexamethasone; VCD, bortezomib, cyclophosphamide and dexamethasone; PFS, progressive free survival; OS, overall survival.

Table 3 Treatment related adverse events

Adverse events	PAD (N=32), n [%]	VCD (N=32), n [%]	P value
Hematologic events			
Neutropenia	21 [65.6]	20 [62.5]	1
Grade 3/4	7 [21.8]	5 [15.6]	0.75
Anemia	20 [62.5]	24 [75]	0.419
Grade 3/4	5 [15.6]	5 [15.6]	1
Thrombocytopenia	12 [37.5]	13 [40.6]	1
Grade 3/4	6 [18.7]	4 [12.5]	0.732
Non-hematological events			
Infection	14 [43.7]	8 [25]	0.188
Grade 3/4	6 [18.7]	4 [12.5]	1
Fatigue	12 [37.5]	7 [21.8]	0.274
Grade 3/4	0	0	
Constipation	8 [25]	6 [18.7]	0.763
Grade 3/4	2 [6.2]	2 [6.2]	1
Diarrhea	7 [21.8]	9 [28.1]	0.774
Grade 3/4	3 [9.3]	3 [9.3]	1
Herpes zoster	5 [15.6]	3 [9.4]	0.509
Grade 3/4	5 [15.6]	3 [9.4]	0.509
Cardiotoxic	2 [6.2]	0	0.492
Grade 3/4	2 [6.2]	0	0.492
Peripheral neuropathy	18 [56.2]	20 [62.5]	0.799
≥ Grade 2	5 [15.6]	7 [21.8]	0.75

PAD, bortezomib, doxorubicin and dexamethasone; VCD, bortezomib, cyclophosphamide and dexamethasone.

Table 4 Univariate and multivariate analysis of the prognosis factors for survival in all the patients

Variables	OS			
	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	OR (95% CI)	P value
Gender, male	0.779 (0.356–1.706)	0.533	0.69 (0.294–1.619)	0.394
Elevated LDH	2.966 (1.287–6.833)	0.011	2.715 (1.184–6.223)	0.018
ALB <35 g/L	3.212 (1.106–9.332)	0.032	2.980 (1.021–8.699)	0.046
ISS II/III	1.916 (0.864–4.248)	0.109	*	*
DS II/III	1.362 (0.408–4.544)	0.615	0.817 (0.209–3.194)	0.772
CR yes/not	0.530 (0.212–1.328)	0.176	0.617 (0.243–1.564)	0.309
β 2-MG >5.5 mg/L	1.314 (0.571–3.026)	0.521	1.432 (0.594–3.451)	0.424

*, ISS was not included as a variate in this multivariate analysis. LDH, lactate dehydrogenase; ALB albumin; DS, Durie-Salmon staging system; ISS, international staging system; CR, complete response; β 2-MG, β 2 microglobulin; PFS, progression free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval.

and ALB level (<35 g/L *vs.* normal) were associated with poor OS (HR=2.966, 95% CI, 1.287–6.833, P=0.011 and HR=3.212, 95% CI, 1.106–9.332, P=0.032).

In the multivariate analysis for OS, the risk of death increased for the patients with high LDH (OR=2.715, 95% CI, 1.184–6.223, P=0.018). And ALB <35 g/L was also an independent factor associated with short OS (OR=2.980, 95% CI, 1.021–8.699, P=0.046).

Other factors, such as DS, CR and β 2-MG were not associated with the OS (Table 4).

Discussion

Recently, with the use of novel agents, such as bortezomib, thalidomide and lenalidomide, better outcomes have been achieved in elderly patients with MM. Generally, regimens such as MPT, MPV, MPR and Rd were recommended as the frontline induction therapy to elderly patients, however, for some specific reasons, the combination of PAD or VCD which was initially designed for younger patients was more frequently used in China, especially for elderly patients aged under 75 years. Until now, very few clinical trials were compared head to head with PAD and VCD regimen in MM. Recently, a phase III trial data showed that VCD was favorable to PAD as induction therapy in transplant-eligible patients. But in this study, the dosage of dexamethasone was higher in VCD group than that in the PAD group (9). Some phase II trials showed that PAD or VCD induction therapies in all cohorts (both young and elderly) can dramatically improve the outcome in MM, with

an ORR (at least PR) of 88–90% and a CR rate of 40% (5,10,11). But no study comparing those two regimens has been performed for transplant-ineligible patients. It was the first time we focused on the elderly patients with MM in our hospital who received either PAD or VCD as frontline treatment.

In elderly patients with either MPB or MPT induction therapy, the ORR could reach 71–80%, including 20–30% CR (12–14). In our study, with PAD or VCD, the ORR (at least PR) of all the 64 elderly myeloma patients was 93.7%, including 32.8% CR. The result was better than that of the literatures. The younger age (mean age was 67 years) and better physical condition in our study might be the reason. In 2011, a report from the European Myeloma Network (EMN) points out that personalized therapy should be made in elderly MM according to the patient's age and vulnerability (15). In 2015, IMWG proposed GA score to evaluate patients' fitness (7). It is necessary to evaluate the effectiveness of different chemotherapy and dosage in each subset in elderly patients. In this study, we only focus on the fit elderly patients. Since this study is a retrospective one, it is difficult to collect all the required data for GA; a simple definition of fit was used. We believe that it is reasonable to perform a prospective, randomized clinical trial to further confirm the results of the studied cohort. In the future study, GA score should be used to precisely define the fit sub-group.

No significant difference was observed between the PAD and VCD group's ORR and CR (90.6% versus 96.8% and 37% versus 28%, respectively). Unlike younger

patients, very few patients in our group could complete the whole eight scheduled cycles of treatment, due mostly to the tolerability. The median treatment cycles were four, reflecting that in fit elderly patients, although could receive intense triplet agents, a shortened induction cycle was still suggested. A way to improve tolerability which might be considered; Reeder et al modified the regimen to a once-weekly schedule of bortezomib. Even after modification, results reached an ORR of 93% and a VGPR of 60%. In addition, only a few dose reductions or treatment interruption were required in the modified schedule (11).

At present, prognostic factors of MM patients include both host factors and disease factors, such as gender, ALB, LDH, cytogenetics, DS stage and ISS. ISS stage which was based on serum 2-microglobulin and ALB, could classify the patients into three risk groups (I/II/III), with median survivals of 62, 44 and 29 months, respectively (16). In our study, ISS appears to be less helpful in predicting the OS, which was also proved by several other reports (17,18). It was suggested that with bortezomib based induction, the poor impact of ISS III on the survival rate might be abrogated; however, further prospective clinical trials are warranted. Of note, in our univariate and multivariate Cox analysis, low ALB (one parameter of the ISS) became an independent factor predicting poor survival; concurrent with a recent study led by Chen *et al.* who also reported that initial low serum ALB increased mortality risk in MM (P=0.029) (19). In our study, another important finding revealed that elevated LDH was strongly associated with short survival during both univariate and multivariate analysis. The elevated serum LDH level commonly reflected an aggressive disease, a high proliferation rate, and a high tumor load. Even in the era of the novel agent use, high LDH remain an independent prognostic factor for poor OS (20). In the year 2015, IMWG has remodified the ISS for MM. In the revised international staging system (R-ISS), LDH was combined as a new parameter to ISS (21).

As for the adverse events, PAD and VCD groups showed a similar safety profile. The most common non-hematologic toxicities included: fatigue, infection, constipation, diarrhea, nausea and herpes zoster; which were comparable to the previous reports. We reported a lower incidence of herpes zoster (9.4–15.6%), as compared with the literatures (13–22%) (22,23), which might be attributed to the routine anti-viral therapy after year 2010 in our hospital. PN is another frequent adverse event of bortezomib. Peng *et al.* performed a meta-analysis of 34 clinical trials, which reported a PN incidence in all grades and high grade of

33.9% and 8.1%, respectively (24). In our cohort, the incidence rate was little higher, 56.2–62.5% for all grades and 15.6–21.8% for grade ≥ 2 . Furthermore, in this study, about 20% dose adjustment and skipping was associated with PN. The difference in ethnic and genetic background or the frailty of elderly patients might be the reason. Even during later treatments where the dosage of bortezomib was reduced in the patients with PN; the curative effect was not affected. Interestingly, some trials affirmed PN being associated with an improved survival. The higher response rate and a longer time to progression were observed in PN experienced patients when compared with those who did not (25,26). In order to avoid adverse events such as PN in the future, weekly or subcutaneous administration of bortezomib will perhaps start to see more common use. This study will surely be worth a try in our center in the future.

In conclusion, bortezomib-based triplet regimens were tolerable and efficacious in fit elderly patients with NDMM. There was no substantial difference between PAD group and VCD group for either outcomes or safety. Low ALB and high LDH were independent prognostic factors in elderly patients, even in the era of the novel agents.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tcr.2017.06.17>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethic Committee of Ruijin Hospital (2014 NO 59) and written informed consent was obtained from all patients.

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