

Original Article

Bortezomib Plus Dexamethasone as the Induction Therapy in Newly Diagnosed Multiple Myeloma Patients: A Phase II Study in Thai Patients

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Abstract: We conducted a phase II study using bortezomib plus dexamethasone (Vel/Dex) as the induction therapy in fifteen consecutive newly diagnosed myeloma patients who were eligible for autologous stem cell transplant. Bortezomib 1.3 mg/m² was administered on days 1, 4, 8 and 11, along with dexamethasone 40 mg orally on day 1-4 and 8-11 of a 21-day cycle for 4 cycles. Twelve male and three female patients were enrolled; the median age was 60 years. Of the 14 evaluable patients, 6 patients (42.9%) achieved complete remission after 4 cycles of Vel/Dex. The overall response rate was 85.8%. Nine patients received DCEP chemotherapy for stem cell mobilization with the median number of CD34+ cells collected of 11.4×10^6 /kg. Eight patients successfully underwent upfront autologous stem cell transplant (ASCT). At the time of this analysis, four patients have died from progressive disease. Two-year overall survival of the whole group was 73.3%. Vel/Dex regimen was very well tolerated. Only one patient was not able to complete 4 cycles. Most common grade 3 or 4 toxicities were anemia (46%) and thrombocytopenia (33.3%). Other serious adverse events were colonic pseudoobstruction (1 case), pneumonia (2 cases) and staphylococcal endocarditis (1 case). We conclude that Vel/Dex is a highly active induction regimen for newly diagnosed myeloma patients who are planned for high-dose therapy and ASCT.

Key Words : ● Multiple myeloma ● Bortezomib ● Dexamethasone ● Stem cell transplantation

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Multiple myeloma (MM) is still an incurable malignant disease despite the introduction of high-dose chemotherapy and autologous stem cell transplantation (ASCT) since the late 1980's.¹ New treatment strategies are in need to improve response rate, prolong remission

duration as well as survival. In patients who are planned for ASCT, choices of induction therapy are limited by stem cell toxicity and potential leukemogenicity of many chemotherapeutic agents. Avoidance of alkylating agents prior to stem cell harvest is generally recommended,² making combination chemotherapy with anthracycline and corticosteroid, such as VAD (vincristine, adriamycin and dexamethasone)³ or C-VAMP (cyclophosphamide, vincristine, adriamycin and methyprednisolone),⁴ the regimens of choice for induction therapy used by many

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centers. This induction chemotherapy is usually administered for 3-4 cycles to obtain maximum response before stem cell collection is done.⁵ Unfortunately, true complete remission (CR) is rare with the induction therapy alone.³⁷ Although complete remission is not a prerequisite for ASCT,⁸ a recent analysis in 1,000 patients who underwent an intensive chemotherapy program called "total therapy" has demonstrated that 38% of patients had resistant diseases that did not respond to standard treatment before transplant. This group of patients got worse outcomes and shorter survival than those who responded well to induction therapy.⁹ Therefore, a new strategy to improve the rate and quality of response before transplant should be beneficial in all myeloma patients.

Several preclinical and phase I-II clinical studies have shown that bortezomib, a first-in-class proteasome inhibitor, is very effective in treating relapsed and/or refractory myeloma.¹¹ Combination therapy with bortezomib and dexamethasone or other chemotherapeutic agents also improve the response rates both in vitro and in vivo.¹² The side effects of bortezomib are very manageable and do not exceed those of chemotherapy normally used in these heavily pretreated patients. The encouraging results prompt us to investigate the efficacy of bortezomib plus dexamethasone (Vel/Dex) as induction therapy in newly diagnosed patients in order to obtain minimal disease status before ASCT. We speculate that Vel/Dex is more effective and less cumbersome to administer than VAD chemotherapy frequently used at our institution. Here, we report the results of the first fifteen patients. We found that Vel/Dex induced complete remission in more than one-third of patients and did not interfere with subsequent stem cell collection and transplant procedures. Therefore, it should be considered as a regimen of choice in myeloma patients who are eligible for ASCT.

Material and Methods

Study population

Newly diagnosed myeloma patients, younger than

65 years old, at our institutions were recruited into the study from March to October 2006. The diagnosis was made according the criteria proposed by International Myeloma Working Group.¹³ All bone marrow specimens together with samples for M-protein measurement were reviewed by an expert hematopathologist and one of the investigators (T.N.N.). The patients were excluded if they had received previous chemotherapy other than one cycle of dexamethasone, the ECOG performance status was greater than 2 or they were considered unsuitable for high-dose chemotherapy and transplantation from any reasons. Fifteen patients were planned for the preliminary study.

The study protocol was approved by the Ethical Committee Review Board of each institute. All patients provided written informed consent and the study was conducted according to the Declaration of Helsinki and the Guidelines for Good Clinical Practice.

Treatment regimens

Vel/Dex

Induction therapy was initiated as soon as the written informed consent was obtained. Bortezomib 1.3 mg/m² was administered on days 1, 4, 8 and 11, along with dexamethasone 40 mg orally on day 1-4 and 8-11 of a 21-day cycle for 4 cycles. Subsequent dose reduction of bortezomib to 1.0 mg/m² was allowed if > grade 2 sensory neuropathy had developed.¹⁴ The whole course of induction therapy was given as outpatient-basis unless there were serious adverse reactions that required hospitalization. Prophylactic treatment with an H₂ antagonist or a proton pump inhibitor to avoid steroid-induced dyspepsia or gastritis was prescribed during the whole period of high-dose dexamethasone. Oral acyclovir and co-trimoxazole were also given for herpes zoster and *Pneumocystis jiroveci* prophylaxis, respectively.

Postinduction therapy

At the end of the planned induction therapy, all patients received one course of DCEP chemotherapy as a consolidation treatment regardless of the initial response to Vel/Dex. DCEP was chosen because previous publi-

cations have shown that it is effective in salvaging primary resistant disease,¹⁵ relatively safe to administer and able to mobilize peripheral blood stem cells (PBSC) when used sequentially after VAD induction chemotherapy.¹⁶ Cytapheresis of PBSC was done when total CD34+ count in peripheral blood was over 10/ μ L. Minimum CD34 dose considered sufficient for autologous transplant was 2×10^6 cells/kg. Harvesting sufficient numbers of CD34+ cells for two transplants was encouraged in every patient but no tandem ASCT was planned.

Autologous stem cell transplant was performed within three months after stem cell harvest using intravenous melphalan 200 mg/m² as the conditioning regimen.¹⁷ Patients who could not undergo autologous transplant were offered four additional courses of Vel/Dex until CR or plateau phase was achieved.

Measurement of treatment responses

Each patient was followed at the Hematology Clinic of the participating centers by one of the investigators for disease status and treatment toxicity every 21 days. Complete evaluation for treatment responses were measured after the 4th cycle of Vel/Dex, just before DCEP chemotherapy using the EBMT criteria as previously reported by Blade et al.¹⁸

Data analysis

Complete remission rate (CRR), which was the primary outcome of this study, was calculated as number of patients who achieve CR divided by number of total patients. Ninety-five percent confidence interval of the CRR were also calculated from $CR \pm 1.96SE$ (CR), where $SE(CR) = \sqrt{[CR(1-CR)/n]}$. Survival data was calculated by using Kaplan-Meier methods. Overall survival (OS) was measured from the date of diagnosis to the date of death from any causes. Disease-free survival (DFS) was measured from the date of CR to the date of documented relapse of myeloma or death from any cause in patients who obtain CR.

Results

Fifteen consecutive patients with newly diagnosed

multiple myeloma were enrolled and eligible for the analysis. There were 12 males and 3 females with the median age of 60 years. Seven patients (47%) had stage III disease. All but one presented with anemia and four patients had renal impairment (serum creatinine > 2 mg/dL). The Table 1 shows the baseline characteristics of patients in this study.

Treatment responses

At the time of this analysis, 14 patients completed 4 cycles of induction therapy. One patient received only two cycles of Vel/Dex and was withdrawn from the study because of infective endocarditis. He then received melphalan and prednisolone but unfortunately died from progressive disease 15 months after the diagnosis. Complete responses were observed in 6 patients (complete response rate 43%, 95% confidence interval 17-69%). The overall response rate (including both complete and partial response) was 85.8 percent.

After the completion of induction therapy, nine patients received DCEP chemotherapy for stem cell mobilization. The median number of CD34+ cells collected was 11.4×10^6 cells/kg (range, $7.67-15.59 \times 10^6$ cells/kg). Eight patients successfully underwent autologous stem cell transplantation with high-dose melphalan as conditioning regimen. One patient had elected to defer the transplant until the first relapse.

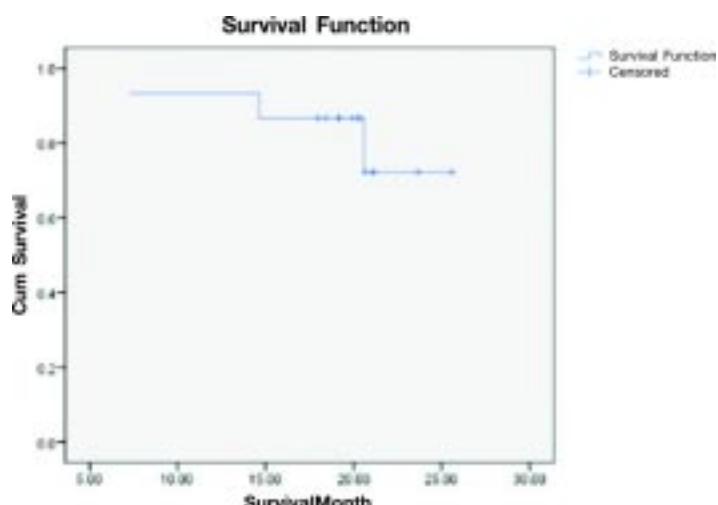
Two additional patients achieved complete or near-complete remission after ASCT. Complete response rate was, therefore, 57.1% for the full treatment protocol. At the time of the analysis, eleven patients are still alive. The 2-year overall survival of the whole group is 73.3% (Figure 1). None of the patients who achieved CR after Vel/Dex or ASCT died from progressive disease. Only one patient (16.7 percent) in this group relapsed at 13.3 months after completion of Vel/Dex induction chemotherapy and was able to be salvaged by second ASCT and thalidomide maintenance. Figure 2 shows the disease-free survival of 6 patients who achieved CR after Vel/Dex.

Treatment toxicity

Vel/Dex was well tolerated in the majority of pa-

Table 1. Baseline characteristics of patients with multiple myeloma in this study

Characteristics	Total N = 15
Age (years)	
Median	60
Range	35-68
Male: Female	12:3
Type of myeloma	
IgG κ : IgG γ	6:4
IgA κ : IgA γ	2:1
Light chain κ : γ	2:0
International Staging System (ISS)	
ISS stage I	3
ISS stage II	5
ISS stage III	7
Serum β_2 -microglobulin (mg/L)	
Mean	5.35
Range	1.3-12.3
Hemoglobin (g/dL)	
Mean	9.07
Range	5.9-14.0
Platelet count (cell/mm ³)	
Mean	234,530
Range	108,000-452,000
Serum creatinine (mg/dL)	
Mean	1.62
Range	0.55-6.04

**Figure 1.** Kaplan-Meier plot showing the overall survival of the whole group

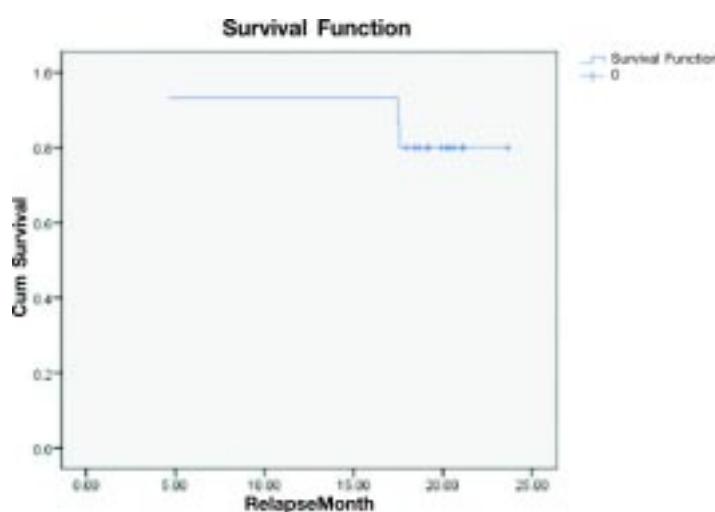


Figure 2. Kaplan-Meier plot showing the disease-free survival of the patients who achieved CR after Bortezomib/dexamethasone (Vel/Dex) induction therapy (n = 6)

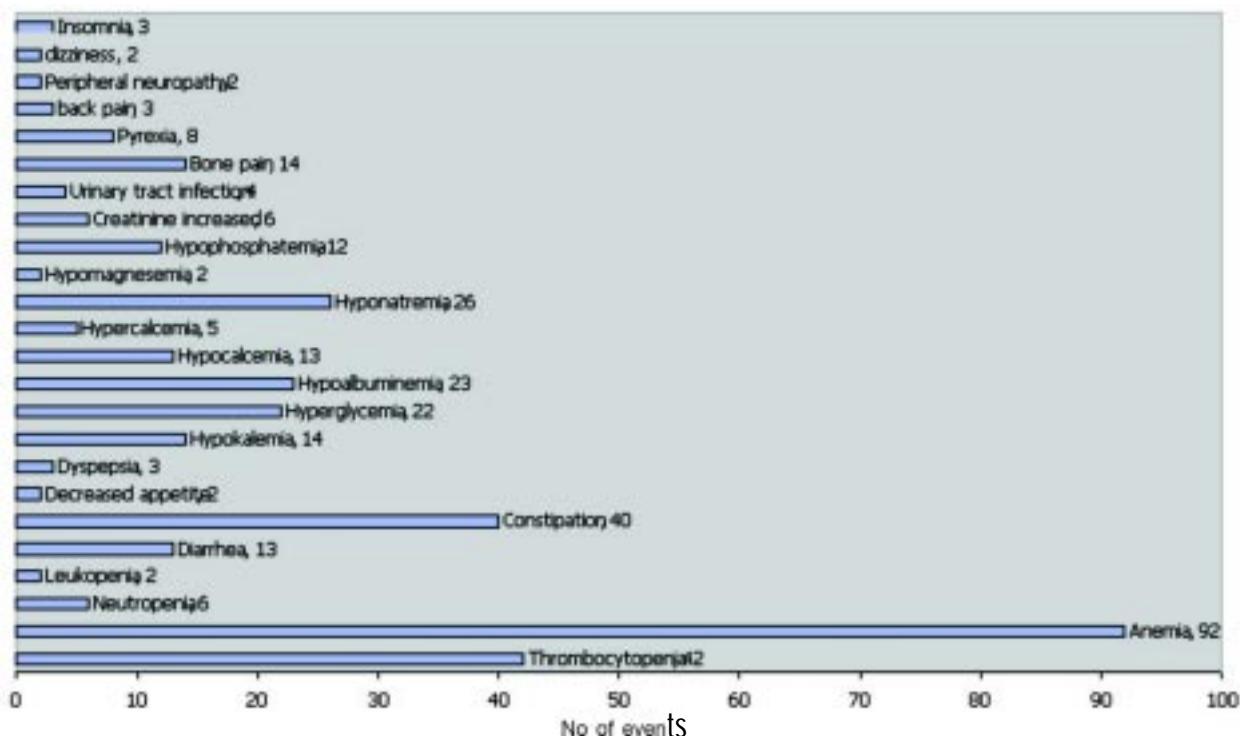


Figure 3. Adverse reactions that occurred more than once in myeloma patients receiving bortezomib and dexamethasone

tients. All but one patient completed four cycles of Vel/Dex. Three doses of bortezomib had to be delayed due to adverse reactions. One patient developed functional obstruction of colon after the third cycle of Vel/Dex that required dose reduction of bortezomib to 1.0 mg/m² in the subsequent cycle. Grade 3-4 adverse reactions as defined by the National Cancer Institute Common Toxicity Criteria occurred in 373 events as shown in the

figure 3. The most common adverse events were hematological toxicities including anemia (92 events) and thrombocytopenia (42 events). One patient developed severe painful polyneuropathy after the fourth cycle of Vel/Dex that precluded him from receiving DCEP chemotherapy.

Severe adverse reactions that required hospitalization occurred in 4 patients including pneumonitis (2

Table 2. Treatment responses after 4 cycles of Bortezomib plus dexamethasone

Response	Number of patients (%)
Complete response	6 (42.9)
Partial response	6 (42.9)
Minimal response	0 (0)
Stable disease	2 (14.2)
Progressive disease	0 (0)

Table 3. Comparison of Vel/Dex and other bortezomib-based induction therapy previously reported in the literature.

Study	Induction regimen	No of cycle	Number of patients	% Response (CR + PR)	% CR pre-SCT	% CR post-SCT
Richardson et al. ²³	Bortezomib alone	6	66	40	10	n/a
Jagannath et al. ²⁴	Vel +/- Dex	6	40	88	6	n/a
Harousseau et al. ²⁵	Vel/Dex	4	48	66	21	33
PETHEMA ²⁶	Bortezomib alternating with Dex	6	40	65	12.5	33
This study	Vel/Dex	4	15	86	43	33

cases), functional obstruction of colon (1 case), Methicillin-resistant staphylococcal endocarditis (1 case) and one episode of febrile neutropenia. None of these events was fatal. The patient who developed colonic dilatation improved significantly only by conservative treatment and rectal tube insertion. Rectal biopsy was later performed and did not show amyloid deposition or pathogens that may explain the symptoms. Bortezomib was thus suspected to be the major cause in addition to hypokalemia and hypomagnesemia that were also observed at the same time. He later received bortezomib at the reduced dose and achieved partial response after induction therapy.

Discussion

Bortezomib is a first-in-class proteasome inhibitor that has been shown to be very active in many types of cancers, including multiple myeloma. In relapsed/refractory patients, bortezomib was demonstrated to be superior to high-dose dexamethasone in a large ran-

domized phase III study (APEX trial).¹⁹ Median time to progression was significantly improved from 3.6 months to 5.7 months ($p<0.001$). Moreover, there were fewer deaths in the bortezomib than the high-dose dexamethasone group at 1-year follow up period. Another phase III study also confirmed the efficacy of bortezomib in this setting and further improved the outcomes by adding pegylated liposomal doxorubicin to the treatment regimen.²⁰ Based on the results of these studies, bortezomib is now considered to be the most effective salvaging agent in relapsed/refractory myeloma.²¹

The role of new antimyeloma agents, such as bortezomib and thalidomide, in the induction phase of newly diagnosed patients is still unclear. It has been suggested that using these agents early in the disease state may translate into a better survival by improving response rate before and after high-dose therapy (HDT) or even replace HDT in patients who are not eligible for SCT.²² Table 3 summarizes the published results of phase II trials using bortezomib with or without dex-

amethasone in previously untreated myeloma patients.²³⁻²⁶ We, here, report the results of a small phase II study using bortezomib with dexamethasone (Vel/Dex) as the induction therapy in Thai patients. In our experience, Vel/Dex induction regimen has a remarkable activity comparable to what have been reported in the literature. Forty-two percents of our patients achieved complete remission defined strictly by negative immunofixation. This exceptionally high CR rate in our experience, as compared to 21% CR rate reported by the IFM group,²⁵ could be due to the higher dose of dexamethasone used in our protocol. Vel/Dex does not interfere with subsequent stem cell mobilization and transplantation. All patients could successfully collect mobilized peripheral blood progenitor cells sufficient for two transplants. The survival data looks very promising as shown by 2-year survival of 77.3%. Interestingly, none of patients who achieved complete remission after Vel/Dex died from disease progression within this time period of the study.

Vel/Dex was generally well tolerated in our patients. The toxicity profile is very similar to the reported experiences in relapsed/refractory patients. All but one patient were able to complete the treatment program. None of the adverse events related to bortezomib was fatal. They were indeed quite manageable with only supportive and symptomatic treatment. Neuropathy is the most disturbing side effect of this regimen. However, only two patients experienced severe neuropathy that required discontinuation of treatment. One patient experienced painful neuropathy after the fourth cycle and one patient developed colonic pseudo-obstruction that may be related to the autonomic neuropathy. Both patients were withheld from bortezomib and received supportive treatment for the symptoms. They were then switched to melphalan/prednisolone for further disease control but achieved only partial response.

In conclusion, Vel/Dex is a highly effective regimen with acceptable toxicity profile and does not affect stem cell mobilization. It should, therefore, be considered

the induction therapy of choice in patients who are planned for upfront ASCT. Whether this high response rate after Vel/Dex can confer a better long-term survival remains to be proven by a large randomized controlled trial.

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การศึกษาระยะที่ 2 ในการใช้ Bortezomib ร่วมกับ Dexamethasone เป็นการรักษาเริ่มแรกในผู้ป่วยมัยอีโลมาคนไทยที่ได้รับการวินิจฉัยใหม่

ธัญญา พงษ์ ณ นคร, พรรณดี วัฒนบุญยงเจริญ, พิมพ์ใจ นิภารักษ์*, สุกร จันท์จารุณี*,
และ ธนาไนท์ อินทร์กำธรชัย

สาขาวิชาโลหิตวิทยา ภาควิชาอายุรศาสตร์ คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย, *สาขาวิชาโลหิตวิทยา ภาควิชาอายุรศาสตร์ คณะแพทยศาสตร์โรงพยาบาลรามาธิบดี มหาวิทยาลัยมหิดล

บทคัดย่อ: คณานักวิจัยได้ทำการศึกษาระยะที่ 2 ใช้ bortezomib ร่วมกับ dexamethasone (Vel/Dex) เป็นการรักษาเริ่มแรก (Induction therapy) ในผู้ป่วยมัยอีโลมาวินิจฉัยใหม่ 15 ราย ซึ่งมีความพร้อมที่จะทำการปลูกถ่ายไขกระดูก สูตรยา Vel/Dex ประกอบไปด้วย bortezomib ในขนาด 1.3 มก/ตรม. พื้นที่ผิวกาย ฉีด ในวันที่ 1, 4, 8 และ 11 ร่วมไปกับ dexamethasone ขนาด 40 มก.ทางปาก ในวันที่ 1-4 และ 8-11 โดยเริ่มยาทุก 21 วัน ทั้งหมด 4 รอบ

ผู้ป่วย 12 รายเป็นเพศชาย ค่ามัธยฐานของอายุ 60 ปี ผู้ป่วย 6 จาก 14 รายที่ประเมินผลได้ (ร้อยละ 42.9) สามารถได้ complete remission หลังรับยาครบ 4 รอบ ส่วนการตอบสนองโดยรวม (complete และ partial) ได้ร้อยละ 85.8 มีผู้ป่วย 9 รายที่ได้รับ ยาเคมีบำบัด DCEP เพื่อเก็บสต์มเซลล์ โดยค่ามัธยฐานของ เซลล์ CD34+ ที่เก็บได้ 11.4 ล้าน เซลล์/กг. และมีผู้ป่วย 8 รายได้รับการปลูกถ่ายสเต็มเซลล์จากตนเองได้สำเร็จ

มีผู้ป่วย 4 รายเสียชีวิตจากโรคลุกลาม โดยมีอัตราการรอดชีวิตที่ 2 ปี ได้ร้อยละ 73.3 ผู้ป่วยส่วนใหญ่ที่หาย Vel/Dex ได้ดี มีเพียง 1 รายที่ได้ยาไม่ครบ ผลข้างเคียงรุนแรง (Grade 3 หรือ 4) คือ โลหิตจางร้อยละ 46 และ เกรดดีเลือดต่ำ ร้อยละ 33.3 ส่วนผลข้างเคียงที่รุนแรงอื่นๆ ได้แก่ ภาวะลำไส้ไม่ทำงาน (1 ราย) ติดเชื้อในปอด (2 ราย) และ ลิ้นหัวใจอักเสบจาก เชื้อ staphylococcus (1 ราย) จึงสรุปว่า Vel/Dex เป็นสูตรยาที่มีประสิทธิภาพสูงในการรักษาเริ่มต้นในผู้ป่วยมัยอีโลมาที่วางแผนจะทำการปลูกถ่ายไขกระดูก

Key Words : ● Multiple myeloma ● Bortezomib ● Dexamethasone ● Stem cell transplantation

วารสารโลหิตวิทยาและเวชศาสตร์บิการโลหิต 2551;18:119-27.

