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. 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, making combination chemotherapy with anthracycline and corticosteroid, such as VAD (vincristine, adriamycin and dexamethasone) or C-VAMP (cyclophosphamide, vincristine, adriamycin and methyprednisolone), the regimens of choice for induction therapy used by many
centers. This induction chemotherapy is usually administered for 3-4 cycles to obtain maximum response before stem cell collection is done. Unfortunately, true complete remission (CR) is rare with the induction therapy alone. Although complete remission is not a prerequisite for ASCT, 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. 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. Combination therapy with bortezomib and dexamethasone or other chemotherapeutic agents also improve the response rates both in vitro and in vivo. 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. 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. 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 pri-
mary resistant disease,\textsuperscript{15} relatively safe to administer
and able to mobilize peripheral blood stem cells (PBSC)
when used sequentially after VAD induction chemo-
therapy.\textsuperscript{16} Cytapheresis of PBSC was done when total
CD34+ count in peripheral blood was over 10/\mu L. Minimum
CD34 dose considered sufficient for autologous trans-
plant was 2x10^6 cells/kg. Harvesting sufficient
numbers of CD34+ cells for two transplants was en-
couraged in every patient but no tandem ASCT was
planned.

Autologous stem cell transplant was performed
within three months after stem cell harvest using intra-
venous melphalan 200 mg/m^2 as the conditioning regi-
men.\textsuperscript{17} Patients who could not undergo autologous trans-
plant 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 mea-
sured after the 4\textsuperscript{th} cycle of Vel/Dex, just before DCEP
chemotherapy using the EBMT criteria as previously
reported by Blade et al.\textsuperscript{18}

Data analysis

Complete remission rate (CRR), which was the pri-
mary 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 ± 1.96SE (CR), where
SE (CR) = \sqrt{CR(1-CR)/n}. Survival data was calcu-
lated 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 characteris-
tics 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 di-
agnosis. Complete responses were observed in 6 pa-
tients (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 pa-
tients received DCEP chemotherapy for stem cell mo-
bilization. The median number of CD34+ cells col-
clected was 11.4x10^6 cells/kg (range, 7.67-15.59x10^6 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 dis-
ese. Only one patient (16.7 percent) in this group re-
lapsed at 13.3 months after completion of Vel/Dex in-
duction 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

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total N = 15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>60</td>
</tr>
<tr>
<td>Range</td>
<td>35-68</td>
</tr>
<tr>
<td>Male: Female</td>
<td>12:3</td>
</tr>
</tbody>
</table>

| Type of myeloma                     |              |
| IgG K: IgG γ                        | 6:4          |
| IgA K: IgA γ                        | 2:1          |
| Light chain K: γ                    | 2:0          |

| International Staging System (ISS)  |              |
| ISS stage I                         | 3            |
| ISS stage II                        | 5            |
| ISS stage III                       | 7            |

| Serum β₂-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/mm³)           |              |
| 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
Bortezomib Plus Dexamethasone as the Induction Therapy in Newly Diagnosed Multiple Myeloma Patients: A Phase II Study in Thai Patients

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

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

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
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 randomized phase III study (APEX trial). 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. Based on the results of these studies, bortezomib is now considered to be the most effective salvaging agent in relapsed/refractory myeloma.

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. Table 3 summarizes the published results of phase II trials using bortezomib with or without dex-
amethasone in previously untreated myeloma patients.\textsuperscript{23,24} 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,\textsuperscript{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.

Acknowledgements

We would like to thank Ms. Kornwipa Poompipkulaya, Ms. Panrudee Panjai and Ms. Natha Tantiwanitchanon for their assistance in data collection. This study was sponsored by Janssen-Cilag (Thailand).

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การศึกษาระดับที่ 2 ในการใช้ Bortezomib ร่วมกับ Dexamethasone เป็นการรักษาเริ่มแรกในผู้ป่วยมัยอิโละมาคนไทยที่ได้รับการวินิจฉัยใหม่

ยัญญพงษ์ ณ นคร, พรณิค วัฒนบุญวงศ์, พิภ์ปลุก นิติกรกุล, นิธิกร จันทร์จารุณี, ยุทธศักดิ์ ชัยรัตน์, ภยานรัตน์ ศักดิ์กิจวิจารย์, ตันนิจจนัส บุญวรรณ

ศัลยศาสตร์ การแพทย์ มหาวิทยาลัยมหิดล

A Phase II Study in Thai Patients

Bortezomib Plus Dexamethasone as the Induction Therapy in Newly Diagnosed Multiple Myeloma Patients:

บทคัดย่อ: คณนาวิจารณ์ได้ทำการศึกษาเวรดับที่ 2 ในการใช้ Bortezomib ร่วมกับ dexamethasone (Vel/Dex) เป็นการรักษาเริ่มแรก (Induction therapy) ในผู้ป่วยมัยอิโลวัณโรคใหม่ 15 ราย ซึ่งมีความรู้สึกที่จะทำการปลูกอย่างไรก็ตาม ผู้ม้า Vel/Dex ประมาณไปด้วย Bortezomib ในร้อยละ 1.3 ของร้อยละ ที่มีผู้ป่วยในร้อยละ 1, 4, 8 และ 11 ร้อยละให้แก่ dexamethasone ขนาด 40 มก. ทว่า บริษัทในร้อยละ 1-4 และ 8-11 โดยเริ่มอาการ 21 วัน ทั้งหมด 4 รอบ

ผู้ป่วย 12 รายเป็นเพศชาย ที่มีอายุป่วย 60 ปี ผู้ป่วย 6 จาก 14 รายที่มีร้อยละ ได้แก่ (ร้อยละ 42.9) สามารถให้ complete remission หลังรับยาตาก 4 รอบ สำหรับดีเอ็มเอซี่ (complete และ partial) ได้รับยาตาก 85.8 ร้อยละ 9 รายที่ได้รับ ยาตากนี้สามารถให้แก่ DCEP เพื่อเก็บเซลล์เลือดโดยคำนวณร้อยละของเซลล์ CD34+ ที่เก็บได้ 11.4 ล้าน เซลล์/ลิตร. และมีผู้ป่วย 8 รายได้รับการปลูกเก็บเซลล์เลือดจากตนเองได้สำเร็จ

มีผู้ป่วย 4 รายเสียชีวิตจากโรคหลักป่วย โดยมีอัตราการสูญเสียที่ 2 ปี ได้ร้อยละ 77.3, ผู้ป่วยส่วนใหญ่ได้มี Vel/Dex ได้ริด 2 ร้อยละ 1 รายที่ได้ริดเกินกว่า 40 และเริ่มตั้งค่า ช่วงการรักษา 46 และเริ่มตั้งค่า ช่วงการรักษา 33.3 ที่รุนแรงที่สุด ได้แก่ การเปลี่ยนแปลง (1 ราย) ติดเชื้อในคอ (2 ราย) และสัมผัสเจ็บผิดมาเกิด เชื้อ staphylococcus (1 ราย) ซึ่งสูตรว่า Vel/Dex เป็นสูตรที่มีประสิทธิภาพสูงในการรักษาเริ่มแรกในผู้ป่วยมัยอิโลวัณโรคที่ต้องการรักษาอย่างไรก็ตาม

Key Words: Multiple myeloma  Bortezomib  Dexamethasone  Stem cell transplantation