

Bortezomib therapy in a real-world setting in patients with relapsed or refractory multiple myeloma

Shang-Yi Huang,¹ Tsai-Yun Chen,² Ching-Yuan Kuo,³ Yeu-Chin Chen,⁴ Sheng-Fung Lin,⁵ Ming-Chih Chang,⁶ Xinzhu Lv,⁷ Betty Yang,⁸ Cheng-Shyong Chang⁹

¹National Taiwan University Hospital, Taiwan; ²National Cheng Kung University Hospital, Taiwan; ³Kaohsiung Chang Gung Memorial Hospital, Taiwan; ⁴Tri-Service General Hospital, National Defense Medical Center, Taiwan; ⁵Kaohsiung Medical University Memorial Hospital; ⁶Mackay Memorial Hospital, Taiwan; ⁷Johnson & Johnson Investment Ltd, Shanghai, P.R. China; ⁸Janssen Medical Affairs, Taiwan; ⁹Chang-Hua Christian Hospital, Taiwan

Corresponding author: Cheng-Shyong Chang, Changhua Christian Hospital, Changhua City, Changhua County, Taiwan.
Fax: 886.47000626.
E-mail: cs4816@gmail.com

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Abstract

Bortezomib is a proteasome inhibitor, approved for treating newly diagnosed and relapsed multiple myeloma (MM). This real-world, multicenter, observational, non-interventional study of bortezomib was designed to collect and analyze prospective data in Taiwanese patients with relapsed or refractory MM. The primary endpoints included clinical effectiveness outcomes (disease response, disease progression [PD], time-to-response, time-to-progression, response duration, and overall survival [OS]). Secondary endpoints were safety and healthcare resource utilization.

Total 100 patients (median [range] age 64.9 [37.0-85.5] years) were enrolled; 47 patients completed the study. Of the withdrawn patients (n=53), there were 48 deaths (PD-related death: n=35, adverse events [AEs]-related: n=12, other reason: n=1), and 5 due to loss to follow-up. Four patients in Cycle 1, 6 patients each in Cycle 2 and 5, 7 in Cycle 3, 10 patients in Cycle 4, 5 patients in Cycle 6, and 3 patients each in Cycle 7 and 8 achieved overall response during the study. Time-to-response was 4.68 months (95%CI: 3.2, NE) and response duration was 10.08 months (95%CI: 2.3, 28.6). Median OS was 9.8 months (95%CI: 3.8, 13.7), and median time-to-progression was 11.3 months (95%CI: 6.2, 20.2). Most common non-hematological AEs were diarrhea (n=32) and hypoesthesia (n=25); most common hematological AE was thrombocytopenia (n=18).

Efficacy and safety profile of bortezomib in Taiwanese patients with MM was similar to global and other Asian population. Study provides a critical insight on use of bortezomib in real-world clinical practice, which can be helpful for Taiwanese healthcare providers' decision-making processes.

Introduction

Incidence of multiple myeloma (MM) is increasing in Asian countries (including Korea and Taiwan) owing to rapid industrialization and increased life span.^{1,2} In Taiwan, the incidence rate of MM is 0.75/100,000 individuals and mortality rate is 0.59/100,000 deaths.¹

The introduction of novel therapeutic agents (proteasome inhibitors and immunomodulatory agents), and advances in supportive care have substantially increased response rates and patient survival in MM.^{3,4} Bortezomib, a proteasome inhibitor, is approved for treating patients with newly diagnosed and relapsed MM in the United States,⁵⁻⁷ and for treating MM in Europe and several other countries (including China).^{8,9} Bortezomib with dex-

amethasone exhibits a favorable safety profile and overall response rate (ORR) of up to 67% in patients with relapsed and refractory MM.^{10,11} Bortezomib is associated with low incidences of thromboembolic complications, and may provide a better safety profile than immunomodulatory agents like thalidomide and lenalidomide.¹² Bortezomib plus melphalan-prednisone has shown to significantly improve outcomes in patients newly diagnosed with MM and ineligible for high-dose therapy.¹³

However, variability between results from clinical trials and those observed in routine healthcare are common in cancer treatment. We report results from an observational study conducted in Taiwan that was designed to evaluate safety and efficacy of bortezomib in patients with relapse or refractory MM, with ≥ 1 prior chemotherapy regimen, in a real-world practice scenario (VELCADE® Observational Study Protocol 26866138MMY4055).

Methods of research

Participants

Taiwanese patients (of either sex) aged ≥ 18 years, with relapsed or refractory MM and ≥ 1 prior chemotherapy regimen were enrolled. All participating patients had already initiated bortezomib therapy within the approved indications. Patients having contraindications listed in package insert (VELCADE®, registered trademark of Millennium Pharmaceuticals, Inc., Cambridge, USA) and participating in another investigational study of bortezomib were excluded.

Patients received the usual treatment and investigations for their condition and were not exposed to experimental investigations during the study. The prescription of bortezomib was not decided in advance by the VELCADE® Observational Study protocol, and separated from the decision to include the patient in the study. The de-identified patient data were encrypted as dictated by international data protection laws.

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, consistent with Good Clinical Practices and applicable regulatory requirements. The study protocol and informed consent form were reviewed and approved by the Institutional Review Boards and/or Independent Ethics Committee at all sites. All enrolled patients provided written informed consent for their participation in the study.

Study design

This was an observational study conducted in Taiwan (7 sites) to document the use of bortezomib in patients who were initiating bortezomib therapy within the approved indication in a real-world setting. The study was conducted between 23 March 2011 and 24 September 2015.

The duration of the study was set prospectively for 4 years from the date the first patient initiated bortezomib. The patient recruitment period was two years. Data collection occurred at baseline and at the end of each cycle of bortezomib therapy via paper-based case report form (CRF), with the exception of SAEs, which were reported within 24 hours of knowledge of the event to the assigned local operating company designate. All patients were followed up to 2 years post treatment; subsequent therapies for MM were documented during the entire post-treatment survival follow-up period up to two years. For patients who discontinued bortezomib before disease progression (PD) and for those who progressed while on bortezomib treatment, post-treatment follow-

up was continued every 12 weeks. For patients who reinitiated bortezomib, data collection was done as per the bortezomib treatment period documentation process. All concomitant treatments were recorded up to the conclusion of the last cycle.

All bortezomib dosages were eligible for the study. Bortezomib was administered as a 3-5 second bolus intravenous injection through a peripheral or central intravenous catheter followed by a flush with 9 mg/mL (0.9%) sodium chloride solution for injection.

Dose adjustments and cycle delays were at physician's discretion. Bortezomib treatment was withheld at the onset of any Grade 3 non-hematological or any Grade 4 hematological toxicities, excluding neuropathy, and was re-initiated following resolution of toxicity symptoms, at 25% reduced dose (1.3 mg/m² reduced to 1.0 mg/m²; 1.0 mg/m² reduced to 0.7 mg/m²). If the toxicity was unresolved or in case of recurrence, bortezomib was discontinued unless the benefit of treatment clearly outweighed the risk. Management of bortezomib-related neuropathic pain and/or peripheral neuropathy is presented in Table S1. Patients with pre-existing severe neuropathy were treated with bortezomib only after careful risk/benefit assessment.

Concomitant medication

Except investigational compounds, all other concomitant medications (bisphosphonates, colony stimulating factors, erythropoietin, platelet and red cell transfusions, loperamide, prophylactic antiemetic, antineoplastic therapy, antibiotics, and non-steroidal anti-inflammatory agents), anti-MM agents (including systemic corticosteroids, clarithromycin, and thalidomide), and treatments consonant with real-world practice (orthopedic surgery, kyphoplasty, emergency local radiotherapy) were allowed during the study.

Efficacy

The primary endpoint was to evaluate the clinical effectiveness outcomes associated with bortezomib (disease response, disease progression, time-to-response, time-to-progression, response duration, and overall survival [OS]). Disease response was classified as complete response (CR), near CR (nCR), very good partial response (VGPR), partial response (PR), and minimal response (MR), stable disease (SD) or PD. The ORR was defined as the proportion of patients with CR, nCR, VGPR, PR, and MR. The methods and criteria used to evaluate the disease responses were chosen and recorded by the physician. Commonly used response criteria included the EBMT criteria,¹⁴ Southwest Oncology Group criteria,¹⁵ and the M-protein criteria¹⁶ for disease response.

Disease progression included PD and relapsed CR (RCR). Time-to-response (from first dose of bortezomib to first response [CR/nCR/PR/MR]); response duration (from first response to first documented PD [determined as the first indication of progression, *e.g.* sufficient elevation of M-protein, new skeletal event, *etc.*], RCR, or death); time-to-progression (from first dose of bortezomib to first documented PD or RCR); and OS (from first dose of bortezomib to death) were also assessed.

Safety

Safety assessments included monitoring of treatment-emergent adverse events (TEAEs), skeletal events (fractures, irradiation of bone, surgery on bone, spinal cord compression), clinical laboratory parameters, electrocardiograms, vital sign measurements, and physical examination. All AEs were assessed using the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE v3.0) and were monitored through 30 days after the last bortezomib dose.

Health care resource utilization

Assessments included number of bortezomib dosages (in mg per m² of body surface area [BSA]) and duration of each cycle, emergency visits, number and duration of hospitalization, therapeutic procedures (e.g., surgery), diagnostic radiography and laboratory procedures, concomitant medications used (including over-the-counter and prescription medications).

Statistical analysis

Since this observational study was designed to generate data for informative purposes, it was descriptive than comparative, and no formal hypotheses were tested in this study. The sample size was mainly determined by pragmatic considerations. Total 100 patients who were initiating bortezomib therapy were to be enrolled. Analyses were carried out on all-patients analysis set (all patients enrolled and treated with bortezomib). Safety analyses were performed on patients who received ≥ 1 dose of bortezomib (safety population).

All statistical analyses were performed using SAS[®] version 9.4 (Cary, NC, USA). The continuous endpoints were summarized descriptively. The number and percentage of patients for the different response categories were tabulated and two-sided 95% confidence intervals (CI) presented. Estimates of the time-to-event endpoints (response duration, OS, and time-to-progression) were obtained using the Kaplan-Meier method. Safety and healthcare resource utilization parameters were summarized descriptively.

Results

Demographics and baseline characteristics

Total 47 of 100 enrolled patients completed the study and 53 were withdrawn from the study (including 48 deaths [PD-related deaths: n=35, AE-related deaths: n=12, death due to other reason: n=1, heart failure]), loss to follow-up: n=5). All enrolled patients received ≥ 1 dose of bortezomib. Of the 100 patients, 49 were men; the median age was 64.9 years (range 37.0-85.5), with 50 patients ≥ 18 to <65 years of age and 50 patients ≥ 65 years of age. Most patients had advanced disease (Stage IIIA as per Durie-Salmon criteria) at baseline (Table 1).

Prior therapies and concomitant medications

The majority of patients received chemotherapy (n= 80) or hormone therapy (n=77) prior to study entry. The most frequently (≥ 50 patients) used prior chemotherapy medication was thalidomide (n=57) while the most frequently (≥ 40 patients) used prior hormonal medication were dexamethasone (n=49) and prednisone (n=43) (Table S2).

The most frequently (≥ 50 patients) used concomitant medications were dexamethasone (n=79), acetaminophen (n=60) and thalidomide (n=59). Subsequent to the last bortezomib cycle, 58 patients received chemotherapy (thalidomide: n=22, cyclophosphamide: n=9, melphalan and lenalidomide: n=5 each, bortezomib: n=4, other drugs: n=19), 47 patients received hormonal therapy, 9 patients received immunotherapy and 1 patient received radiotherapy for treating MM.

Treatment compliance

Majority of patients received bortezomib 1.3 mg/m² dose during the study (Cycle 1: 87%, Cycle 2: 80%, Cycle 3: 84%, Cycle 4: 82%, Cycle 5: 84%, Cycle 6: 81%, Cycle 7: 82%, Cycle 8: 81%; Cycle 9-11: 100%) followed by 1.0 mg/m² dose (Cycle 2: 5%,

Cycle 3, 4 and 5: 3% each, Cycle 7 and 8: 1% each). Nine patients had one-dose adjustments during the study (Cycle 1: n=3, Cycle 2: n=2, Cycle 3: n=1, Cycle 4: n=2, Cycle 6: n=1) while one patient each in Cycle 2 and Cycle 3 had dose adjustments done thrice and twice respectively.

Efficacy

Patients had disease assessment done during Cycle 1 (7 patients) to Cycle 8 (3 patients). Four patients in Cycle 1, 6 patients each in Cycle 2 and 5, 7 in Cycle 3, 10 patients in Cycle 4, 5 patients in Cycle 6, and 3 patients each in Cycle 7 and 8 achieved OR (CR+ nCR + VGPR + PR + MR) during the study; of these, 1 patient each in Cycle 2, 4, 5 and 8 and 2 patients in Cycle 6 achieved CR and 2 patients each in Cycle 1, 4, and 5. One patient in Cycle 7 had PD. One patient each in follow-up visit 1, 2, 4, 6,

Table 1. Demographics and baseline characteristics (all patients analysis set).

| Characteristics | All-patient analysis set |
|---|--------------------------|
| Women, n (%) | 51 (51) |
| Men | 49 (49) |
| Age, years, median (range) | 64.9 (37.0-85.5) |
| Stage of myeloma at baseline (durie-salmon criteria), n (%) | |
| IA | 2 (2) |
| II | 1 (1) |
| IIA | 7 (7) |
| IIB | 1 (1) |
| IIIA | 32 (32) |
| IIIB | 11 (11) |
| Not available | 46 (46) |
| Stage of myeloma at baseline (ISS Criteria), n (%) | |
| I | 13 (13) |
| II | 22 (22) |
| III | 35 (35) |
| Not available | 30 (30) |
| Type of myeloma, n (%) | |
| Secretory | 95 (95) |
| Non-secretory | 5 (5) |
| New bone lesions at baseline, n (%) | |
| 1 | 4 (4) |
| 2 | 5 (5) |
| ≥ 3 | 19 (19) |
| Not available | 72 (72) |
| Plasma cells in bone marrow, n; median (range) | 72; 42.5 (0.2-98.0) |
| Extramedullary plasmacytoma present, n (%) | 8 (8) |
| Hemoglobin (gm/L), n; median (range) | 95; 9.3 (5.5-15.4) |
| Platelet count ($\times 10^3/\mu\text{L}$), n; median (range) | 94; 171.0 (23.0-610.0) |
| Serum creatinine level, n (%) | |
| <2 mg/dL | 83 (83) |
| ≥ 2 mg/dL | 17 (17) |
| Albumin, n (%) | |
| <3.5 g/dL | 83 (83) |
| ≥ 3.5 g/dL | 17 (17) |
| Serum $\beta 2$ -microglobulin, n (%) | |
| <2.5 mg/dL | 35 (35) |
| 2.5-5.5 mg/dL | 3 (3) |
| >5.5 mg/dL | 6 (6) |

ISS, International staging system; SD, standard deviation.

and 8 achieved an nCR. One patient each in follow-up visit 2, 3 and 7, and 2 patients in follow-up 6 had PD (Table 2).

At the 25th percentile, the time-to-response was 4.68 months (95% CI: 3.2 months, not evaluable) (Table 3, Figure 1), while the response duration was 10.08 months (95% CI: 2.3, 28.6 months) (Table 3, Figure 2). Overall, 35 patients with response had PD (including death due to PD) or RCR and 65 patients maintained response during the study. At 25th percentile, the time-to-progression was 11.28 months (95% CI: 6.2, 20.2 months) (Table 3, Figure 3). Data from 54 patients were censored for the Kaplan-Meier estimates of death, and 46 patients died during the study or follow-up. At the 50th percentile, the median survival time was 30.72 months (95% CI: 18.2 months, not evaluable) (Table 3, Figure 4).

Time-to-response was defined as the duration in days between the start date of bortezomib therapy and the date of first documented evidence of response including CR, nCR, VGPR, PR or MR. Median time-to-response could not be evaluated.

Duration of response was defined as the duration from the date on which response documented until PD, RCR, and death due to PD among patients who had a response. Time to progression was defined as the duration in days between the start of bortezomib therapy and the date of first documented evidence of confirmed PD (including death due to PD) or RCR.

Safety

Overall, 99 patients experienced ≥ 1 AE; of these, 57 patients had TEAEs (possibly related [n=30], probably related [n=19], very likely related [n=8]). Total, 57 patients experienced ≥ 1 serious TEAE; 50 patients had severe/life-threatening/fatal TEAEs. There were 12 deaths during the study; 6 due to TEAEs (septic shock and sepsis [n=3], acute respiratory distress syndrome [n=2], and acute myocardial infarction, plasma cell myeloma, pyrexia, lacunar infarction, pneumonia and acute respiratory failure, and respiratory failure [n=1]), and 6 due to PD (Table 4). Total, 71 patients had TEAEs persisting while 14 patients had TEAEs resolved at the end of the study. Of the 99 patients, 19 patients received ≥ 1 concomitant medication for a TEAE during the study.

The most commonly reported (>30% patients) TEAEs was diarrhea (n=32). Total 14 patients reported peripheral neuropathy (Table 4). The most common treatment-emergent SAEs were pneumonia (n=17), sepsis (n=7), pyrexia and septic shock (n=6 each), and herpes zoster (n=5).

Most patients (≥ 62 patients) received only 4 cycles of bortezomib therapy and had routine hematology and biochemistry laboratory evaluations from baseline through Cycle 4. The mean (SD) platelet count decreased from 188.7 (118.3) $\times 10^3/\mu\text{L}$ (baseline, n=94) to 154.3 (108.4) $\times 10^3/\mu\text{L}$ in Cycle 1 (n=96) and increased to

Table 2. Disease response to bortezomib in individual cycles (all patients analysis set).

| Cycle (number of patients) | Response, n (%) | | | | | | | | |
|----------------------------|-----------------|-------------|--------------|---------------|-------------|-------------|-------------|-------------|--------------|
| | OR n (%) | CR n (%) | nCR n (%) | VGPR n (%) | PR n (%) | MR n (%) | SD n (%) | PD n (%) | RCR n (%) |
| 1 (n=100) | 4 (4.0) | 0 | 0 | 1 (1.0) | 3 (3.0) | 0 | 1 (1.0) | 2 (2.0) | 0 |
| 2 (n=88) | 6 (6.8) | 1 (1.1) | 0 | 1 (1.1) | 1 (1.1) | 3 (3.4) | 0 | 1 (1.1) | 0 |
| 3 (n=76) | 7 (9.2) | 0 | 0 | 3 (3.9) | 1 (1.3) | 3 (3.9) | 0 | 0 | 0 |
| 4 (n=62) | 10 (16.1) | 1 (1.6) | 0 | 1 (1.6) | 7 (11.3) | 1 (1.6) | 2 (3.2) | 2 (3.2) | 0 |
| 5 (n=38) | 6 (15.8) | 1 (2.6) | 0 | 1 (2.6) | 4 (10.5) | 0 | 0 | 2 (5.3) | 0 |
| 6 (n=32) | 5 (15.6) | 2 (6.3) | 1 (3.1) | 0 | 2 (6.3) | 0 | 0 | 0 | 0 |
| 7 (n=27) | 3 (11.1) | 0 | 0 | 0 | 3 (11.1) | 0 | 0 | 1 (3.7) | 0 |
| 8 (n=26) | 3 (11.5) | 1 (3.8) | 0 | 1 (3.8) | 0 | 1 (3.8) | 0 | 0 | 0 |

CR, complete response; nCR, near complete response; MR, minimal response; OR, overall response; RCR, relapse from CR; PR, partial response; PD, disease progression; SD, stable disease; VGPR, very good partial response.

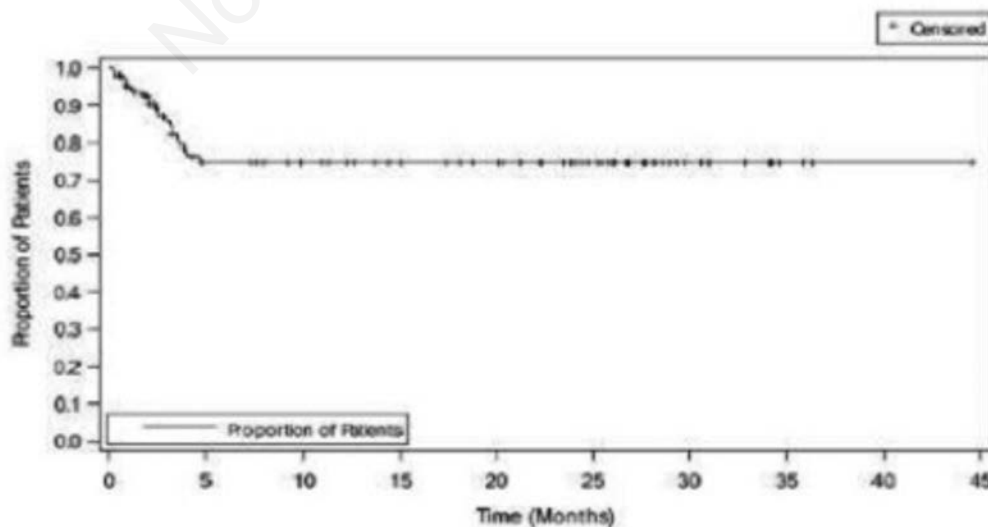


Figure 1. Median time-to-response following bortezomib therapy in Taiwanese patients with MM (all patients analysis set).

164.5 (105.9)×10³/μL in Cycle 2 (n=86), 177.4 (109.8)×10³/μL in Cycle 3 (n=71), and 176.2 (79.8)×10³/μL in Cycle 4 (n=61). Mean changes from baseline were statistically significant (P<0.05) for decreases in eosinophils and basophils (Cycle 1), and lymphocytes (Cycles 1, 2, 4), increases in neutrophils, monocytes, hematocrit, hemoglobin levels and red blood cell counts (Cycles 1-4). Additionally, significant increases (P<0.05) from baseline were observed for white blood cell counts in Cycles 2 and 4. The mean serum lactate dehydrogenase levels were significantly (P<0.05)

Table 3. Summary of Kaplan-Meier estimates (all patients analysis set).

| No. of patients | Event n (%) | Censored n (%) | Percentile Months | 95% CI |
|---|-------------|----------------|-------------------|-------------------|
| Time-to-response^a | | | | |
| 100 | 22 (22) | 78 (78) | 75 | NE |
| | | | 50 | NE |
| | | | 25 | 4.68 (3.2, NE) |
| Duration of response^b | | | | |
| 22 | 9 (41) | 13 (59) | 75 | NE (28.6, NE) |
| | | | 50 | NE (10.1, NE) |
| | | | 25 | 10.08 (2.3, 28.6) |
| Time-to-progression^c | | | | |
| 100 | 35 (35) | 65 (65) | 75 | NE |
| | | | 50 | NE (30.1, NE) |
| | | | 25 | 11.28 (6.2, 20.2) |
| Overall survival | | | | |
| 100 | 46 (46) | 54 (54) | 75 | NE |
| | | | 50 | 30.72 (18.2, NE) |
| | | | 25 | 9.84 (3.8, 13.7) |

^aTime-to-response was defined as the duration in days between the start date of bortezomib therapy and the date of first documented evidence of response including CR, nCR, VGPR, PR or MR.; ^bDuration of response was defined as the duration from the date on which response documented until PD, RCR, and death due to PD among patients who had a response; ^cTime-to-progression was defined as the duration in days between the start of bortezomib therapy and the date of first documented evidence of confirmed PD (including death due to PD) or RCR; All percentages are calculated based on number of patients.

Table 4. Safety profile of bortezomib in Taiwanese patients with MM (all patients analysis set).

| Characteristics | All patients analysis set (N=100) n (%) |
|--|---|
| Total number of patients with ≥1 AE | 99 (99) |
| Number of deaths | 18 (18) |
| TEAEs leading to death | 12 (12) |
| Disease progression | 6 (6) |
| AE relationship for TEAEs leading to death | |
| Not related | 6 (6) |
| Possibly related | 3 (3) |
| Probably related | 3 (3) |
| Number of patients with SAEs | 12 (12) |
| Maximum severity of SAE | |
| Grade 3 | 4 (4) |
| Grade 4 | 5 (5) |
| Grade 5 | 3 (3) |
| Most common TEAEs (>10% patients) | |
| Diarrhea | 32 (32) |
| Hypoesthesia | 25 (25) |
| Cough | 24 (24) |
| Pyrexia | 23 (23) |
| Insomnia | 22 (22) |
| Constipation | 19 (19) |
| Thrombocytopenia | 18 (18) |
| Pneumonia | 18 (18) |
| Decreased appetite | 17 (17) |
| Dizziness | 17 (17) |
| Back pain | 16 (16) |
| Fatigue | 16 (16) |
| Herpes zoster | 15 (15) |
| Neuropathy peripheral | 14 (14) |
| Vomiting | 13 (13) |
| Malaise | 13 (13) |
| Upper respiratory tract infection | 13 (13) |
| Abdominal pain | 12 (12) |
| Abdominal distension | 11 (11) |
| Edema peripheral | 11 (11) |
| Hypokalemia | 11 (11) |
| Rhinorrhoea | 11 (11) |
| Rash | 11 (11) |

TEAE, treatment-emergent adverse event.

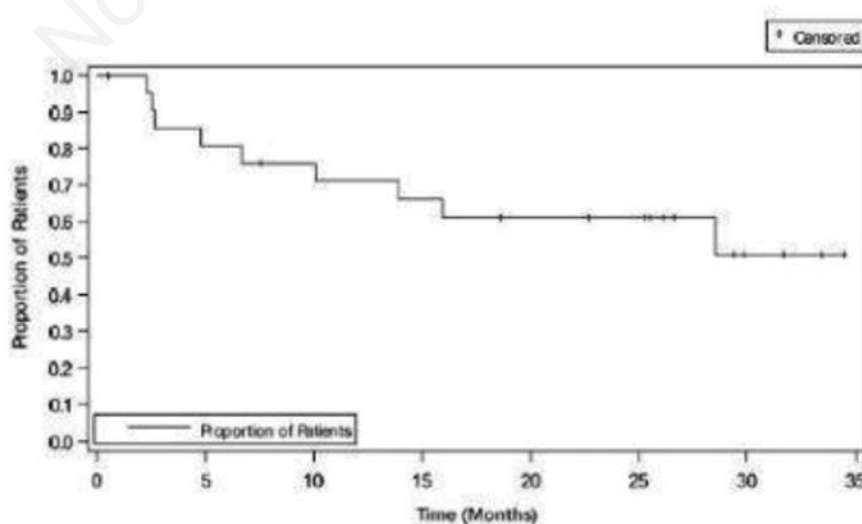


Figure 2. Median duration of response following bortezomib therapy in Taiwanese patients with MM (all patients analysis set).

increased from baseline to Cycle 3, while the mean serum total protein levels were significantly ($P<0.05$) decreased from baseline to Cycle 4. There were no other clinically meaningful and significant mean changes from baseline in any of the chemistry parameters over time.

There were statistically significant decrease ($P<0.05$) in mean changes from baseline through Cycle 8 in IgG protein ($n=8-33$) and through Cycle 4 in IgA protein ($n=14-17$). There were no other statistically significant mean changes from baseline to Cycle 9 in any of the efficacy laboratory evaluations.

At baseline, the mean (SD) percentage of plasma cells in bone marrow of 72 patients was 42.3 (28.0)% and 19 patients had ≥ 3 bone lesions. For patients with available data (C1, $n=1$; C3, 2; C4, $n=5$; C6, $n=3$; C8, $n=2$) one patient in Cycle 1 had 43.2% plasma cells in bone marrow and 1 patient in Cycle 5 had 11.6% plasma

cells in bone marrow while 2 patients each in Cycle 3 and 8, 5 in Cycle 4 and 3 in Cycle 6, the mean plasma cells in bone marrow was $<7\%$.

Eight patients had extramedullary plasmacytoma at baseline. The most commonly (≥ 3 patients) used methods for evaluation were physical exam ($n=3$) and other methods (including echocardiogram and x-ray; 3 patients) while plasmacytoma biopsy was performed for 4 patients. Following bortezomib treatment, only 4 patients (Cycle 2: $n=3$; Cycle 4: $n=1$) had extramedullary plasmacytoma (confirmed by biopsy). Fewer patients ($n=7$) had ≥ 1 new skeletal event with spinal cord compression (Cycle 2 and 3: $n=2$ each) being the most common new skeletal event during the study.

Healthcare resource utilization

Total 42 patients had emergency visits and 50 patients were

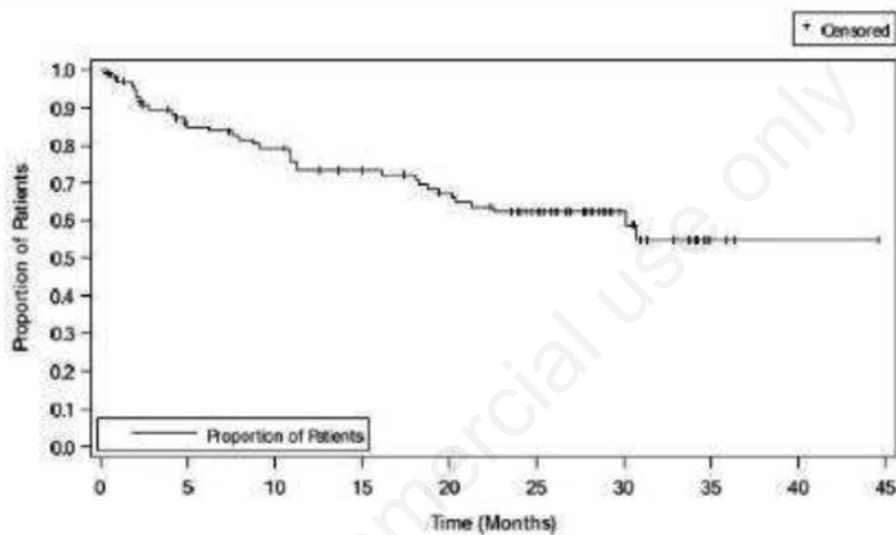


Figure 3. Median time-to-progression following bortezomib therapy in Taiwanese patients with MM (all patients analysis set).

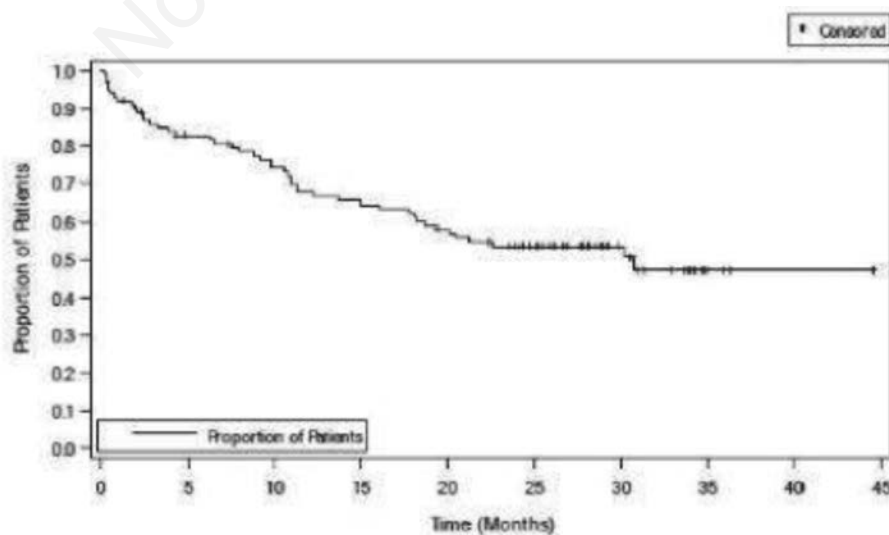


Figure 4. Overall survival following bortezomib therapy in Taiwanese patients with MM (all patients analysis set).

hospitalized during the study; however, the number of patients with emergency visits decreased from Cycle 1 (n=25) to 8 (n=4) and further during follow-up 3 (n=1). Also, the number of patients who were hospitalized decreased from Cycle 1 (n=17) to 8 (n=4), and follow-up 1 (n=1). Most of these patients were hospitalized for infection (Cycle 1: n=6, Cycle 2: n=7, Cycle 3, Cycle 7, and follow-up 1: n=1 each). No patient was hospitalized for blood transfusion. The mean (SD) number of hospital days was 18.1 (19.2) days; the mean (SD) number of hospital days varied from 12.3 (9.1) to 25.0 (20.1) days (except in Cycle 8: 6.3 [4.7] days). Overall, 91 patients received ≥ 1 blood transfusion during the study. However, the number of patients receiving ≥ 1 blood transfusion decreased from Cycle 1 (n=27) to 9 (n=1), and follow-up 1 (n=1). The number of patients with diagnostic radiography did not vary greatly from Cycles 1 to 4 and ranged from 4 to 6. One patient in Cycle 8 had diagnostic radiography. No patients had diagnostic radiography in Cycles 5 to 7 and Cycles 9 to 11. Residual/recurrence disease was reported in 1 patient each in Cycle 1, 2 and 3, and 2 patients in Cycle 4.

Discussion

Proteasome inhibitors and immunomodulators have therapeutic advantages over conventional strategies, and hence have emerged as a more feasible treatment option for patients with relapsed/refractory MM, particularly those ineligible for high-dose chemotherapy.^{17,18} Several studies have established the efficacy and safety of bortezomib in the Caucasians,^{10,11,13,19-21} and Asians.^{22,23} However, as clinical trials are restrictive in their setup and design,²⁴ the current observational study was designed to simulate the real-world practice scenario and help insight into the therapeutic feasibility of bortezomib in Taiwanese patients with relapsed or refractory MM.

The majority of patients received bortezomib 1.3 mg/m² and did not require dose adjustment during the study. Literature suggests that maximum inhibition (73-83%) of 20S proteasome is observed at this dose.²⁵ The response duration (10.08 months) is consistent with that observed in the Caucasian populations (12.7 months).²⁰

This being a real-world study, investigators only reported results from assessments that they considered necessary at each visit, thus only a very small number of patients had any kind of assessment done at each cycle. Data was hence insufficient to derive the ORR for this population. Nevertheless, cycle-wise ORR was determined to evaluate the effectiveness of bortezomib in these patients.

Of the evaluable Taiwanese patients with MM, the majority demonstrated PR; this is consistent with earlier studies in Asian population (25%-42%).^{22,23} Furthermore, although SD status was not achieved in most patients, those demonstrating PD were notably few. These findings are consistent with global and Asian studies,^{20,22,23} which supports the therapeutic advantage of bortezomib when introduced early as salvage treatment in the course of disease. It should be noted here that although studies have demonstrated that higher response quality is associated with longer response duration and survival,²⁶⁻²⁸ not all studies show an absolute benefit of achieving CR, and there may exist a subgroup of patients who may obtain prolonged survival often without ever achieving CR.^{29,30} For such a subgroup treatment emphasizing depth of response may be too toxic and less beneficial. In such cases the goal is to obtain the best possible response while managing toxicities. However, as most of the patients received only 4 cycles of treatment, the efficacy could not be assessed completely

in the present study. Although agents including bortezomib show high anti-MM activity, most patients with MM eventually relapse, including those who achieved CR with the initial therapy. However, in the current study no patient had RCR during the study or follow-up. Thus, the efficacy results of this observational study in real-world setting demonstrates the utilization and feasibility of bortezomib, confirming its use in Taiwanese patients with relapse or refractory MM.

The safety profile of bortezomib was similar to that observed with other global studies and no unexpected safety findings were observed. Although thrombocytopenia and osteoporosis are the most common TEAEs reported, 6 both events were low in this study (thrombocytopenia: n=18; osteoporosis: n=1). There were very few clinically meaningful and significant ($P < 0.05$) mean changes from baseline through Cycle 8 in the hematology laboratory parameters and most of them were related to MM. There were few emergency visits and hospitalizations during the study. Deaths due to TEAEs, SAEs and AEs leading to discontinuation were also low in this study. Thus, it indicates that bortezomib produces a manageable toxicity profile in the Taiwanese population.

According to the rule of reimbursement by Taiwan national insurance, all the MM patients can use maximum 8 cycles of bortezomib before disease progression. Therefore, most of the patients in this study could use full dose bortezomib 1.3 mg/m² before disease progression or withdrawal that demonstrates tolerability of bortezomib in RR MM patients. Study results suggest that approximately 40% patients require more than 4 cycles of bortezomib and approximately 25% patients need more than 8 cycles.

One limitation of this observational study was that the majority of patients (≥ 62 patients) received only 4 cycles of bortezomib therapy and hence the complete efficacy and safety profile of bortezomib could not be assessed. Being a non-interventional study, investigators were not obliged to perform every assessment at every visit listed in the protocol, thus the number of patients who had effectiveness or health care resource utilization assessment done was very low throughout the study.

Conclusions

The current observational study supports that the efficacy and drug toxicity profile of bortezomib in Taiwanese patients with MM is similar to global and Asian population in real-world practice. Also, study provides a critical insight on use of bortezomib in real-world clinical practice, which can be helpful for Taiwanese health-care providers' decision-making processes.

References

1. Lee JH, Lee DS, Lee JJ, et al. Multiple myeloma in Korea: past, present, and future perspectives. Experience of the Korean multiple myeloma working party. *Int J Hematol* 2010;92:52-7.
2. Huang SY, Yao M, Tang JL, et al. Epidemiology of multiple myeloma in Taiwan: increasing incidence for the past 25 years and higher prevalence of extramedullary myeloma in patients younger than 55 years. *Cancer* 2007;110:896-905.
3. Rollig C, Knop S, Bornhauser M. Multiple myeloma. *Lancet* 2015;385:2197-208.
4. Bianchi G, Anderson KC. Understanding biology to tackle the disease: multiple myeloma from bench to bedside, and back. *CA Cancer J Clin* 2014;64:422-44.

5. Food and Drug Administration. Velcade (bortezomib) I. Prescribing Information. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021602s031s032lbl.pdf Accessed: October 2017.
6. Kane RC, Bross PF, Farrell AT, Pazdur R. Velcade: U.S. FDA approval for the treatment of multiple myeloma progressing on prior therapy. *Oncologist* 2003;8:508-13.
7. Kane RC, Dagher R, Farrell A, et al. Bortezomib for the treatment of mantle cell lymphoma. *Clin Cancer Res* 2007;13:5291-4.
8. Myeloma Euronet. Treatment with bortezomib. Available from: <http://www.myelomaeuronet.org/en/multiple-myeloma/treatment-withbortezomib.php> Accessed: October 2017.
9. LoRusso PM, Venkatakrishnan K, Ramanathan RK, et al. Pharmacokinetics and safety of bortezomib in patients with advanced malignancies and varying degrees of liver dysfunction: phase I NCI Organ Dysfunction Working Group Study NCI-6432. *Clin Cancer Res* 2012;18:2954-63.
10. Jagannath S, Barlogie B, Berenson J, et al. A phase 2 study of two doses of bortezomib in relapsed or refractory myeloma. *Br J Haematol* 2004;127:165-72.
11. Richardson PG, Barlogie B, Berenson J, et al. Extended follow-up of a phase II trial in relapsed, refractory multiple myeloma: final time-to-event results from the SUMMIT trial. *Cancer* 2006;106:1316-9.
12. Lonial S, Richardson PG, San Miguel J, et al. Characterisation of haematological profiles and low risk of thromboembolic events with bortezomib in patients with relapsed multiple myeloma. *Br J Haematol* 2008;143:222-9.
13. San Miguel JF, Schlag R, Khuageva NK, et al. Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. *N Engl J Med* 2008;359:906-17.
14. Blade J, Samson D, Reece D, et al. Criteria for evaluating disease response and progression in patients with multiple myeloma treated by high-dose therapy and haemopoietic stem cell transplantation. Myeloma subcommittee of the EBMT. European Group for Blood and Marrow Transplant. *Br J Haematol* 1998;102:1115-23.
15. Thompson JL, Hansen LA. Thalidomide dosing in patients with relapsed or refractory multiple myeloma. *Ann Pharmacother* 2003;37:571-6.
16. Myeloma.org. Concise review of the disease and treatment options. Available from: <https://www.myeloma.org/sites/default/files/images/publications/UnderstandingPDF/cisereview.pdf> Accessed: October 2017.
17. Katznel JA, Hari P, Vesole DH. Multiple myeloma: charging toward a bright future. *CA Cancer J Clin* 2007;57:301-18.
18. Bae J, Munshi NC, Anderson KC. Immunotherapy strategies in multiple myeloma. *Hematol Oncol Clin North Am* 2014;28:927-43.
19. Richardson PG, Barlogie B, Berenson J, et al. A phase 2 study of bortezomib in relapsed, refractory myeloma. *N Engl J Med* 2003;348:2609-17.
20. Richardson PG, Sonneveld P, Schuster M, et al. Extended follow-up of a phase 3 trial in relapsed multiple myeloma: final time-to-event results of the APEX trial. *Blood* 2007;110:3557-60.
21. Richardson PG, Sonneveld P, Schuster MW, et al. Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. *N Engl J Med* 2005;352:2487-98.
22. Lin M, Hou J, Chen W, et al. Improved response rates with bortezomib in relapsed or refractory multiple myeloma: an observational study in Chinese patients. *Adv Ther* 2014;31:1082-94.
23. Igarashi N, Chou T, Hirose T, et al. Bortezomib and dexamethasone for Japanese patients with relapsed and refractory multiple myeloma: a single center experience. *Int J Hematol* 2010;92:518-23.
24. Singal AG, Higgins PD, Waljee AK. A primer on effectiveness and efficacy trials. *Clin Transl Gastroenterol* 2014;5:e45.
25. Curran MP, McKeage K. Bortezomib: a review of its use in patients with multiple myeloma. *Drugs* 2009;69:859-88.
26. Barlogie B, Anaissie E, Haessler J, et al. Complete remission sustained 3 years from treatment initiation is a powerful surrogate for extended survival in multiple myeloma. *Cancer* 2008;113:355-9.
27. Hoering A, Crowley J, Shaughnessy JD, et al. Complete remission in multiple myeloma examined as time-dependent variable in terms of both onset and duration in Total Therapy protocols. *Blood* 2009;114:1299-305.
28. Niesvizky R, Richardson PG, Rajkumar SV, et al. The relationship between quality of response and clinical benefit for patients treated on the bortezomib arm of the international, randomized, phase 3 APEX trial in relapsed multiple myeloma. *Br J Haematol* 2008;143:46-53.
29. Rajkumar SV, Fonseca R, Dispenzieri A, et al. Effect of complete response on outcome following autologous stem cell transplantation for myeloma. *Bone Marrow Transplant* 2000;26:979-83.
30. Pineda-Roman M, Bolejack V, Arzoumanian V, et al. Complete response in myeloma extends survival without, but not with history of prior monoclonal gammopathy of undetermined significance or smouldering disease. *Br J Haematol* 2007;136:393-9.