Velcade® Safety and Effectiveness Study: A Case Series of Seven Filipino Adult Patients Diagnosed with Relapsed or Refractory Multiple Myeloma

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ABSTRACT

Multiple myeloma is the second most prevalent blood cancer after non-Hodgkin's Lymphoma. It represents only 1% of all cancers but contributes to 2% of all cancer deaths. Multiple myeloma is still classified as a non-curable disease and its management involves chemotherapy, radiotherapy and bone marrow transplantation with the aim of prolonging survival. Bortezomib (Velcade®) is a new type of anti-myeloma drug and clinical trials show that patients under treatment have around 80% to 90% overall response rate. Hence bortezomib was placed on a monitored release status by the BFAD in June of 2005 and had required post-marketing surveillance study. It is therefore the objective of the study to describe the safety and effectiveness of bortezomib among Filipino patients with relapsed or refractory multiple myeloma.

This is a case series study observing the effects of bortezomib use in seven adult Filipino diagnosed with multiple myeloma. Study participants were included if they were determined to have a relapsed multiple myeloma, who have received at least one prior therapy or have demonstrated disease progression during the last therapy. The 3 week treatment cycle for bortezomib (Velcade®) begun at recommended dose of 1.3 mg/m^2 administered as an intravenous bolus injection twice weekly for two weeks (days 1, 4, 8, and 11) followed by a 10-day rest period (days 12-21). It was administered as a 3-5 second bolus intravenous injection through a peripheral or central intravenous catheter followed by a flush with 0.9% sodium chloride solution for injection. Eight cycles of bortezomib (Velcade®) therapy were recommended for patients presenting response to treatment. Follow-up period lasted as long as the patient used bortezomib or if the patient has completed the 6 to 8 cycles of treatment. Overall, treatment responses to bortezomib (Velcade®) range from a stable disease (2 patients) to minimal or partial response (4 patients) based on EBMT classifications. Two non-serious and seven serious adverse events, similar to previous clinical trials were reported.

Based on the analysis of the seven eligible case reports on clinical experience with bortezomib (Velcade®) in Filipinos with multiple myeloma, the effectiveness and safety profile is consistent with the previous studies conducted and the approved product label. The expected improvement in the activities of daily living was observed in this set of patients. No new safety signal is observed.

Key Words: bortezomib, Filipino, multiple myeloma

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Introduction

Multiple myeloma (MM), also known as plasma cell myeloma or Kahler's disease, is a plasma-cell neoplasm characterized by skeletal destruction, renal failure, anemia and hypercalcemia.[1] It is the second most prevalent blood cancer after non-Hodgkin's Lymphoma with 14,600 new cases per year in the United States.[2] Although the disease represents only 1% of all cancers, it contributes to 2% of all cancer deaths. Multiple myeloma is still classified as a non-curable disease and its management involves chemotherapy, radiotherapy and bone marrow transplantation with the aim of prolonging survival.[2,3]

Bortezomib (Velcade®, formerly known as PS-341) is a new type of anti-myeloma drug. It is a boronic acid dipeptide, protease inhibitor where the boron atom binds the catalytic site of the 26S proteasome with high affinity and specificity. Bortezomib affects the ability of myeloma cells to interact with the bone marrow microenvironment and has been shown to reduce tumour growth in vivo.[4,5] A phase II study of 54 patients comparing two doses of bortezomib (1.0 and 1.3 mg/m2) showed 23% versus 35% response rates, respectively (p>0.05). Another phase II study consisted of 202 heavily pretreated patients and of the 188 patients eligible for evaluation, complete response occurred in 3% and partial responses occurred in 25%.[6,7]

In the Philippines, the common treatment for the disease is melphalan - prednisone (MP) combination, vincristine – adriamycin - dexamethasone (VAD) combination, thalidomide and bone marrow transplantation. Unfortunately, only about 40-50% of patients respond to treatment regimens melphalan-prednisone (MP) and VAD with median survival of 3 years and 2 year remission period. Clinical trials involving bortezomib have shown that patients under treatment have around 80% to 90% overall response rate.

Compassionate Use Program (CUP) was approved by Bureau of Food and Drugs or BFAD (currently known as

Philippine Food and Drug Administration or FDA) in 2004 to give Filipino patients access to the drug as a treatment for multiple myeloma as it holds support of effectiveness among patients who are not responding to the usual treatment. The program involved ten patients and its report was submitted to Philippine FDA on November 2006 and subsequently approved by the agency on December 2007. Bortezomib was placed on a monitored release status by the agency in June of 2005; hence, the need for a post-marketing surveillance study. It is therefore the objective of the study to describe the safety and effectiveness of bortezomib among Filipino patients with relapsed or refractory multiple myeloma.

This is a case series study observing the effects of Bortezomib use in seven eligible adult Filipinos diagnosed with Multiple Myeloma. This is a post-markekrting surveillance study (PMS), which is required by the local FDA. As per local regulation, the number of patients to be included in this PMS is at least 10% of patients who received the product during the period of 2006 – 2008.

This is an observational study, and management of patients enrolled is based on routine clinical practice in the Philippines and based on the approved product label. Study participants were included if they were determined to have a relapsed multiple myeloma, who have received at least one prior therapy or have demonstrated disease progression during the last therapy.

Exclusion criteria included a history of hypersensitivity to bortezomib, boron and mannitol, peripheral neuropathy or neuropathic pain grade 2 or higher as defined by National Cancer Institute (NCI) Common Terminology Criteria for Adverse Event (CTCAE) version 3, uncontrolled or severe cardiovascular disease, including myocardial infarction within 6 months of enrolment, New York Heart Association (NYHA) class II to IV heart failure, uncontrolled angina, clinically significant pericardial disease or cardiac amyloidosis, platelet count less than 50,000 per cubic millimeter, absolute neutrophil count less than 500 per cubic millimeter, serum alanine aminotrasferase (ALT) or aspartate aminotrasferase (AST) greater than 3x the upper limit of the normal range, total serum bilirubin greater than 2x the upper limit, presently in a clinical trial or was included in a clinical trial for the past 6 months, and/or pregnant women or patients refusing contraception during the program.[5]

All patients signed an informed consent prior to joining the study.

Bortezomib (Velcade®) Dosing

The 3 week treatment cycle for bortezomib (Velcade®) was begun at the recommended dose of 1.3 mg/m^2 administered as an intravenous bolus injection twice weekly for two weeks (days 1, 4, 8, and 11) followed by a 10-day rest period (days 12-21). It was administered as a 3-5 second bolus intravenous injection through a peripheral or central intravenous catheter followed by a flush with 0.9% sodium chloride solution for injection. Eight cycles of bortezomib (Velcade®) therapy was recommended for patients presenting response to treatment. Follow-up period lasted as long as the patient used bortezomib or if the patient has completed the 6 to 8 cycles of treatment.[8]

Occurrence of any grade 3 non-hematologic or grade 4 hematologic toxicity and/or neuropathy warrants discontinuation of bortezomib (Velcade®) therapy. However, if resolution of symptoms is documented, therapy can be reinitiated at a 25% reduced dose (1.3 mg/m^2/dose reduced to 1.0 mg/m^2/dose; 1.0 mg/m^2/dose reduced to 0.7 mg/m^2/dose).[8]

Dosing and dose modifications were based on approved product label, and the decisions on what laboratory examinations to request were left to the physicians' discretion. A case-report form was filled-up by the investigator based on data availability in the patient records. Patient's response will be monitored at the end of treatment or any time during the last exposure of the patient to the treatment drug, if treatment was not completed. Adverse events were assessed, documented and reported within required regulatory timelines.

Ethical Concerns

This study protocol and other related documents including informed consent forms were approved by the Philippine Food and Drug Administration (FDA, previously known as Bureau of Food and Drug or BFAD), and by the Ethical Review Board (ERB)/Institutional Review Board (IRB) of the participating institutions prior to the conduct of the study. These institutions were University of Santo Tomas Hospital, St. Luke's Medical Center, Chong Hua Medical Center and Riverside Medical Center.

Case Presentation

There were 7 eligible patients who were followed-up in this study and who were included in this cases series.

Case 1

A 65-year-old male diagnosed with stage IIIA multiple myeloma who received previous treatment regimen of melphalan-prednisone combination. His European Group for Blood and Marrow Transplantation or EBMT response criteria during the previous treatment was rated as progressive disease. Baseline Karnofsky Performance scale was rated 60 and peripheral neuropathy grading was rated grade 1. The patient received 6 cycles of Bortezomib (Velcade®).

His EBMT classification of response was rated partial response after 6 cycles of treatment. The Karnofsky Performance scale was rated 90 after 6 cycles and the peripheral neuropathy grading was rated grade 1 after the follow-up visit. The patient was reported at one point to

have been hospitalized due to thrombocytopenia with bleeding. This particular adverse event was also assessed by the investigator as life threatening. The event was eventually resolved and was classified as related by the investigator.

Case 2

A 54-year-old male diagnosed with stage IA multiple myeloma who received previous treatment regimen of thalidomide. Baseline Karnofsky Performance scale was rated 60 and peripheral neuropathy grading was rated grade 2 with pain. Despite of this neuropathic pain condition, the attending physician gave bortezomib (Velcade®) to the patient and the patient completed the 8 cycles treatment of Bortezomib (Velcade®).

His EBMT classification of response was rated stable after 8 cycles of treatment. The Karnofsky Performance scale was rated 50 after 8 cycles and the peripheral neuropathy grading was rated grade 1 after the follow-up visit. The patient experienced serious adverse events of pulmonary congestion, acute renal failure, and febrile neutropenia. These events prompted patient's hospitalization. The investigator assessed these events as not related to bortezomib.

Case 3

A 67-year-old male diagnosed with stage IIIA multiple myeloma who received previous treatment regimen of melphalan-prednisone combination. His EBMT response criteria during the previous treatment was rated as progressive disease. Baseline Karnofsky Performance scale was rated 50 and peripheral neuropathy grading was rated grade 1. The patient received 6 cycles of bortezomib (Velcade®).

The Karnofsky Performance scale was rated 80 after 6 cycles and the peripheral neuropathy grading was rated grade 1 after 6 cycles of treatment. The patient experienced no adverse event.

Case 4

A 46-year-old female diagnosed with stage IIIA multiple myeloma who received previous treatment regimen of melphalan-prednisone combination. Her EBMT response criteria during the previous treatment was rated as partial response. Baseline Karnofsky Performance scale was rated 90 and peripheral neuropathy grading was rated grade 1. The patient received 4 cycles of bortezomib (Velcade®).

Her EBMT classification of response was rated partial response after 4 cycles of treatment. The Karnofsky Performance scale was rated 90 after 4 cycles and the peripheral neuropathy grading was rated grade 1 after the follow-up visit. The patient experienced two adverse events: herpes zoster and pneumonia, which were both assessed as related by the investigator. The occurrence of pneumonia was classified as serious, as this prompted the hospitalization of the patient. Both events were subsequently resolved.

Case 5

A 77-year-old male diagnosed with stage IIIA multiple myeloma who received previous treatment regimen of melphalan-prednisone combination. His EBMT response criteria during the previous treatment was rated as minimal response. Baseline Karnofsky Performance scale was rated 60 and peripheral neuropathy grading was rated grade 1. The patient received 6 cycles of bortezomib (Velcade®).

His EBMT classification of response was rated minimal response after 6 cycles of treatment. The Karnofsky Performance scale was rated 90 after 6 cycles and the peripheral neuropathy grading was rated grade 1 after the follow-up visit. Patient experienced three adverse events, two of which were classified as serious and one was considered as non-serious. The serious adverse events prompted patient's two hospitalizations. The first hospitalization was due to vomiting six times with dehydration. The second hospitalization was due to mulitple events such as urinary tract infection with increase blood creatinine level, hypercalcemia, vomiting and dizziness. These serious adverse events had resolved, and were considered by the investigator as not related to bortezomib. The non-serious adverse event was diarrhea. The event resolved and was assessed by the investigator as related.

Case 6

A 34-year-old male diagnosed with stage IIA multiple myeloma who received previous treatment regimen of melphalan-prednisone combination. His EBMT response criteria during the previous treatment was rated as stable disease. Baseline Karnofsky Performance scale was rated 70 and peripheral neuropathy grading was rated grade 1. The patient received 2 cycles of bortezomib (Velcade®).

His EBMT classification of response was rated minimal response after 2 cycles of treatment. The Karnofsky Performance scale was rated 80 after 2 cycles and the peripheral neuropathy grading was rated grade 1 after the follow-up visit. The patient experienced no adverse event.

Case 7

A 77-year-old female diagnosed with stage IIA multiple myeloma who received previous treatment regimen of melphalan-prednisone combination. Her EBMT response criteria during the previous treatment was rated as partial response. Baseline Karnofsky Performance scale was rated 50 and peripheral neuropathy grading was rated grade 2. Despite of the grade 2 neuropathic pain, the attending physician still administered bortezomib (Velcade®). The patient received 2 cycles of bortezomib (Velcade®).

Her EBMT classification of response was rated partial response after 2 cycles of treatment. The Karnofsky

Performance scale was rated 50 after 2 cycles and the peripheral neuropathy grading was rated grade 2 with pain after the follow-up visit. Patient died in a non-institutional environment due to disease progression. No autopsy was done.

Discussion

A total of eligible 7 patients were enrolled in the program from among thirty-six (36) patients who used the drug from 2006 to the end of the study in July 2008. This number of enrolled subjects represents nineteen percent (19%) of the total number of patients who received the product during this period, in compliance with the local health regulation. The patients' mean age was 60.00 (SD ±16.43) years with the youngest being 34 years and oldest 77 years old (Table 1). One death occurred during the study period due to progressive disease. There were two patients with grade 2 neuropathic pain who were given bortezomib by their attending physicians. One patient remained with grade 2 neuropathic pain after two cycles of treatment while the other patient had grade 1 neuropathic pain after completing the whole 8 cycles of bortezomib treatment.

Of the 7 patients, four of them have completed the 6-8 cycle treatment, while one patient has only received 4 cyles and two have two cycle treatment. Though the latter three patients showed either minimal or partial response, reasons for not completing the treatment were not provided. It is presumed that the cause might be due to drug cost. As this is a PMS study, the drug is bought by the patient, as prescribed by the attending physician.

The average baseline Karnofsy Performance score among the patients was 63 (SD ± 13.80) meaning the adults can take care of most of their personal requirements but will require some help. After treatment cycles with bortezomib (Velcade®), the average end-visit Karnofsy Performance score increased to 76(SD ±18.13). This increase of 13 in performance score after the follow-up period may be small but those who showed increased scores are now able to care for themselves although they may not be able to do normal activity or work.

Overall, treatment responses to bortezomib (Velcade®) range from having stable disease (1 patient) to minimal (2 patients) or partial response (3 patients) based on EBMT classifications. One patient died and the cause of death was reported as multiple myeloma. One patient was not assessed however based on the EBMT criteria. This is consistent with the pivotal study done in 2007 where bortezomib (Velcade®) showed 32% partial response rate.

There are a total of two non-serious and six serious adverse events that were legitimately considered in this study (Table 2). Drug related non-serious adverse events reported included diarrhea and herpes zoster. In clinical trials for bortezomib (Velcade®), diarrhea and herpes zoster have been observed at rates of 52% and 12%, respectively.[4] On the other side, five adult patients reported serious adverse events and three legitimate cases contain conditions assessed by investigator as drug related. Occurrence of the adverse events are similar to those reported in different clinical trials and no new event was considered to be a safety concern.

Table 2. Serious adverse events reported by investigators during the study

Reported Serious Adverse Events	Causality Assessment by Investigator	Outcome
Hospitalization due to vomiting (six times) with dehydration	related	recovered
Hospitalization due to multiple events: increased creatinine, urinary tract infection and hypocalcemia, vomiting and dizziness	related	recovered
Hospitalization due to pulmonary congestion, acute renal failure and febrile neutropenia	not related	Persisting*
Hospitalization due to febrile neutropenia	not related	Persisting*
Hospitalization due to a life-threatening condition: thrombocytopenia with bleeding	related	recovered
Hospitalization due to pneumonia	not related	recovered

*Persisting at the time of the report

Table 1. Clinical characteristics of the seven adult Filipino patients diagnosed with Multiple Myeloma who received treatment cycles of Bortezomib (Velcade®) from 2006 to 2008

Age/Sex	No. of Cycles	Karnofsky Performance[9]		Peripheral neuropathy		Best Response
		Baseline Score	End Visit Score	Baseline Grading	End Visit Grading	EMBT*[10]
65 / Male	6	60	90	Grade 1	Grade 1	Partial Response
54 / Male	8	60	50	Grade 2 w/ pain	Grade 1	Stable Disease
67 / Male	6	50	80	Grade 1	Grade 1	Not assessed
44 / Female	4	90	90	Grade 1	Grade 1	Partial Response
77 / Female	6	60	90	Grade 1	Grade 1	Minimal Response
34 / Male	2	70	80	Grade 1 w/ pain	Grade 2 w/ pain	Minimal Response
77 / Female	2	50	50	Grade 2 w/ pain	Grade 2 w/ pain	Partial Response

European Group for Blood and Marrow Transplantation Criteria

Conclusion

Based on the analysis of the 7 case reports of clinical experience of bortezomib (Velcade®) in Filipinos with multiple myeloma, the effectiveness and safety profile is consistent with the previous studies conducted and the approved product label. The expected improvement in the activities of daily living was observed in this set of patients. No new safety signal is observed.

Declaration of interests

The study was sponsored by Janssen Pharmaceutical Companies of Johnson and Johnson Philippines and the following investigators were involved: (1) Honorata Baylon, MD (St. Luke's Medical Center) (2) Priscilla Caguioa, MD (University of Santo Tomas Hospital), (3) Catherine Rosales, MD (St. Luke's Medical Center), (4) Leilanie Cabahug, MD (Chong Hua Hospital) and (5) Evna Lin Agraviador, MD (Riverside Medical Center). This publication is based on the cases reported by the aforementioned investigators. Editorial support for the writing of this manuscript was provided by Noel Juban, Jr., MD, of the University of the Philippines-Manila, and this publication was funded by Janssen Pharmaceutical Companies of Johnson and Johnson Philippines. Dr. Josephine Tolentino is currently the Medical Education Manager of Janssen Philippines.

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