Advances in the Treatment and Management of Filipino Patients with Multiple Myeloma: From Deadly to Chronic Disease with Possibility of Remission

Erwin G. Benedicto, MD, MPH[1], Kristine Joy L. Tomanan, RN[2]
Marvin P. Angeles, RN[1], Carl Abelardo T. Antonio, MD, MPH[3]

Abstract

Background: Multiple myeloma is a malignant proliferation of plasma cells that accumulate in the bone marrow and results in several organ dysfunctions that are debilitating and fatal. For the past 20 years, advances in the understanding of genetic abnormalities, interactions in the bone marrow microenvironment, developments in the diagnosis and staging in myeloma and introduction and incorporation of novel agents early in the disease course have been pivotal in the clinical treatment and management of patients with multiple myeloma. However, the burden associated with the disease, including treatment costs, is significant for Filipino patients as it is still incurable. In the Philippines, the introduction of bortezomib in the market in the last decade have brought hope to many patients by expanding the availability of treatment options, improving quality of life and extending survival.

Methods: This paper documents the proceedings of a forum on multiple myeloma conducted last March 2018 at Makati City. The purpose of the forum was to discuss the major clinical presentations of the disease as well as treatment and management of selected patients. Speakers were hematology and medical oncology experts in the Philippines.

Results: Five cases of multiple myeloma with different clinical presentations and management were discussed: (1) renal insufficiency, (2) easy fatigability, (3) bone pain, (4) autologous stem cell/bone marrow transplantation and (5) coagulopathy. Short videos of selected patients (or their family members) after each presentation was showed, describing their treatment journey with myeloma. Other patients with multiple myeloma who were treated with bortezomib were present in the forum and briefly shared their experiences.

Conclusion: As multiple myeloma is a highly heterogeneous molecular disease, approaches and provision of care will need to be individualized for each patient. Because of its impressive performance, bortezomib is likely to continue being an important part of the clinical treatment and management of Filipino patients with myeloma.

Keywords: multiple myeloma, plasma cell disorders, monoclonal gammopathies, targeted therapy, bortezomib

INTRODUCTION

Multiple myeloma is a malignant proliferation of plasma cells that accumulate in the bone marrow and results in several organ dysfunctions and symptoms[1-3] that are debilitating and fatal.[4] The most prominent clinical features are bone pain or fracture, renal failure, anemia, infections, hypercalcemia and occasionally clotting abnormalities, neurologic symptoms and problems related to hyperviscosity.[3] Myeloma commonly affects the elderly, aged 65-74 years, with 69 years as median age.[5]

Globally, multiple myeloma accounts for around 1% of all cancer cases and 10-15% of hematologic cancers.[1,5] On the other hand, the incidence of multiple myeloma in the Philippines is considered low at 1.1-1.2 per 100,000 compared to the United States (particularly of African American origin), New Zealand, Martinique and Britain.[5,6] In 2015, for both sexes, new cases in the country were estimated at 395 while deaths were recorded at 266.[7] However, the burden associated with the disease, including treatment costs, is significant for Filipino patients as multiple myeloma is still an incurable disease.

[1] *From Johnson & Johnson Philippines, Inc.*
[2] *From Department of Community Development, College of Social Work and Community Development, University of the Philippines Diliman*
[3] *From Department of Health Policy and Administration, College of Public Health, University of the Philippines Manila*

Current management of myeloma involves chemotherapy, radiotherapy and bone marrow transplantation, with the goals of controlling disease and striving for deep responses, thereby prolonging patient survival and maximizing quality of life.[8,9]

For the past 20 years, advances in the understanding of genetic abnormalities present in multiple myeloma cells, alongside interactions in the bone marrow microenvironment, have been pivotal in the diversity of available clinical treatment and management of patients with myeloma.[10-12] In addition, developments in the diagnosis and staging of multiple myeloma contributed to the improvement in better provision of care and patient outcomes.[9] Furthermore, the introduction and incorporation of novel agents, particularly early in the disease course, has resulted to a paradigm shift in the treatment of multiple myeloma.[13] Specifically, the entry of immunomodulatory drugs (especially thalidomide and lenalidomide) and proteasome inhibitors (e.g. bortezomib, carfilzomib) in the last 15 years have been pivotal in improving the median overall survival of patients with myeloma.[14]

In the Philippines, the introduction of bortezomib (Velcade®) in the market since 2006 have brought hope to many patients by expanding the availability of treatment options as well as improving quality of life and outcomes. Bortezomib's effectiveness and safety profile in adult Filipino patients with multiple myeloma as well as improvement in activities of daily living have already been established.[8] Common treatment for the disease used to be melphalan-prednisone (MP) combination, vincristine-adriamycin-dexamethasone (VAD) combination, thalidomide and autologous stem cell (bone marrow) transplantation.[8] More than 10 years later, bortezomib has already become an important part of the frontline clinical treatment and management of Filipino patients with myeloma.

METHODS

This paper documents the proceedings of a forum on multiple myeloma treatment and management organized by Johnson & Johnson Philippines, Inc. last 13 March 2018 at Manila Peninsula Hotel, Makati City. The purpose of the forum was to discuss the major clinical presentations of multiple myeloma as well as treatment and management journey of selected patients. There were approximately 70 attendees of this event.

The program consisted of five (5) brief clinical case discussions with an open forum at the end of each case. The five (5) speaker-lecturers were the following: (1) Dr. Marjorie Ferriols Bravo, currently affiliated with Providence Hospital, Marikina Doctors Hospital and St. Luke's College of Medicine; (2) Dr. Pamela Rose Mancio, affiliated with University of Sto. Tomas Hospital and Asahikawa Medical University Hospital; (3) Dr. Maria Clariza Santos, presently affiliated with Manila Doctors Hospital and University of the Philippines (UP) College of Medicine; (4) Dr. Alma Calavera, currently affiliated with University of the East-Ramon Magsaysay (UERM) Memorial Medical Center, UERM College of Medicine and The Medical City; and (5) Dr. Jesus Relos, presently affiliated with UP-Philippine General Hospital, Asian Hospital and Medical Center, Makati Medical Center, St. Dominic Medical Center and University of Perpetual Help Rizal. The moderator of the forum is Dr. Ivy Escasa, currently affiliated with UP-Philippine General Hospital, Adventist Medical Center and St. Luke's Medical Center – Global City.

RESULTS

Each speaker presented one (1) remarkable case of multiple myeloma they encountered during clinical practice. Treatment and management done for the patients were briefly discussed. Short videos of selected patients in the case (or his/her family member) were played after every discussion, describing their treatment journey with myeloma. Other patients present in the forum also briefly shared their experience.

Case 1: Renal insufficiency

The patient is a 65-year old female who reported five (5) months of back pain, easy fatigability and weight loss. Anemia with multiple compression deformities on the thoracic and lumbar vertebrae were seen by the orthopedic specialist. Patient also noted drowsiness, decreasing urine output, anorexia and nausea. Significant laboratory results showed low hemoglobin levels at 6.6 g/dl, hypercellular bone marrow with plasmacytosis at 40%, and monoclonal gammopathy at 21.6% (1.75 g/dl). A decreasing trend

on estimated creatinine clearance (ECC) was noted from May to August (from 53 ml/min to 11ml/min). During the same period, increasing levels of serum K (from 5.71 to 6.00 mmol/L) and creatinine (from 1.1 mg/dl to 4.7 mg/dl) were observed. Treatment plan included administration of bortezomib for one (1) cycle. Progress in patient's condition was then observed, with hemoglobin levels improved to 10.2 g/dl, K at 4.50 mmol/L, creatine at 1.57 mg/dl and ECC at 34 ml/min.

Case 2: Easy fatigability

The patient is a 45-year old male who was admitted for easy fatigability. Notable findings from laboratory diagnostics included rouleaux formation in the peripheral blood smear, monoclonal gammopathy and elevated beta-2 macroglobulin levels (14.9 g/dl). Treatment plan consisted of intensive chemotherapy, bortezomib and dexamethasone. Conservative management was pursued; blood transfusion was restrictive and erythropoietin injections were limited. Administration of bortezomib resulted to gradual improvement in the patient's hemoglobin levels (from 8.4 g/dl to 10.7 g/dl).

Case 3: Bone pain

The patient is a 52-year old male who was admitted for bone pain. He complained of worsening back pain, progressing to debilitating until he was mostly bedbound. Thereafter, he was admitted at a local hospital. Significant laboratory findings included anemia and elevated serum creatinine as well calcium levels, in which the patient was advised work up for possible malignancy. He was transferred to a public tertiary hospital for further management. Notable baseline lab results showed low hemoglobin (7.7 g/dl), elevated serum Ca levels (15 mg/dl), creatinine (4.75 mg/dl), monoclonal gammopathy (3.0 g/dl) and multiple lytic lesions on the ribs, humerus, vertebral bodies and compression deformities on T7, T9 and T12. Interventions done included intravenous hydration plus furosemide, erythropoietin injection, dexamethasone pulsing and chemotherapy (bortezomib, cyclophosphamide and dexamethasone). After 4 cycles of chemotherapy, the patient improved from being mostly bedbound to fully active with no performance restrictions. Moreover, his hemoglobin, creatinine and serum Ca returned to normal levels.

Case 4: Autologous stem cell transplantation (Auto SCT)

Five (5) patients (2 males and 3 females) from ages 45 to 65 were identified as eligible for autologous stem cell (bone marrow) transplant. Prior to transplantation, bortezomib was part of the induction regimen of each patient (from as low as 4 cycles to as high as 9 cycles). Very good partial response to complete response were achieved by the patients before auto SCT. All five (5) were able to tolerate the procedure relatively well, with minor and manageable post-operative complications noted (e.g. fever/chills, infection, weakness, mucositis, hematuria, gastrointestinal problems). Four (4) patients are presently in complete remission (one patient for already 2 years) and one (1) is undergoing consolidation.

Currently, autologous SCT is the standard of care for patients with multiple myeloma. Patients who are eligible for transplantation are offered this option because it mobilizes stem cells early, the procedure is more tolerable and cost-effective in the long run (around Php 700,000 including hospitalization to Php 2 million). However, transplant will not cure myeloma but can help increase patients' survival and lengthen their remission. Complete remission is highly possible with auto SCT up to 10 years. Relapse can occur but can be controlled with alkylating medications.

Especially for younger patients (30 years old and above) with multiple myeloma, allogeneic SCT is a promising option. Nevertheless, stem cells from the umbilical cord blood can be difficult to obtain as there is currently no cord blood bank in the Philippines. Another concern is graft versus host disease that can occur as a complication with allogeneic transplantation. Still, costs and benefits of available treatment options must be carefully considered together with patients and their families.

Case 5: Coagulopathy

The patient is a 63-year old female who was admitted for surgical intervention of compartment syndrome. She was seen at the emergency department with swelling and tenderness of the left forearm, limited range of motion but with intact

sensation and good capillary refill. During surgery, because of the uncontrolled bleeding and impending shock that did not respond to standard measures (e.g. blood transfusion, platelet transfusion), the patient's condition was referred to the hematology department and multiple myeloma was suspected. Plasmapheresis was then initiated and bortezomib was also administered perioperatively. Her status improved, and amputation of the affected limb was avoided. Significant laboratory findings showed low hemoglobin levels (8.4 g/dl), serum creatinine (1.12 mg/dl), monoclonal gammopathy (5.9 g/dl) and lytic change on the superior angle of scapula and degenerative changes in the spine (C3-C4, C5-C6, C6-C7, L5-S1). While recuperating from surgery, long-term management of the patient's myeloma was pursued, with the inclusion of bortezomib among treatment. Currently, the patient can already move her left arm with full range of motion with some but manageable limitations in finger dexterity.

DISCUSSION

Although multiple myeloma remains an incurable disease, advances in drug development and treatment, especially with the introduction of immunomodulatory drugs (especially thalidomide and lenalidomide) and proteasome inhibitors (e.g. bortezomib, carfilzomib) in the last 15 years have improved patients' median overall survival.[14,15] These have also resulted in a paradigm shift in the treatment and management of myeloma, especially when used early in the disease course.[13,16]

As multiple myeloma is not homogenous[17] but a highly heterogeneous molecular disease[18] new treatments and drugs will continue to develop that can selectively target proteins or modify signaling pathways that are relevant in the pathogenesis of individual patients. Several classes of agents currently used in the treatment of myeloma include immunomodulatory drugs, proteasome inhibitors, histone deacetylase inhibitors, monoclonal antibodies, alkylators and steroids.[19] These drugs are often combined as doublets, triplets or multiple drug regimens, which makes choosing the optimal therapy at diagnosis and relapse, challenging.[19] The five cases presented in the forum demonstrates the varying clinical manifestations associated with myeloma, each managed differently.

Since its approval by the US Food and Drug Administration in 2003 and Committee for Proprietary Medicinal Products of the European Union in 2004, bortezomib has been an integral part of multiple myeloma therapy.[20] It is a highly selective, reversible inhibitor of the 26S proteasome that plays a key role in the regulation of protein degradation in the cell (Figure 1).[21] Through proteasome inhibition, bortezomib acts via multiple mechanisms to suppress tumor survival pathways as well as arrest tumor growth, spread and angiogenesis.[22] The drug is the first proteasome inhibitor approved for clinical use in multiple myeloma because of its notable performance and was considered as a major advance in the treatment of this disease.[23] A 2016 Cochrane meta-analysis review of bortezomib found that patients receiving the drug benefited in terms of overall survival (OS), progression free survival (PFS) and response rate compared to those who did not receive bortezomib.[23] This was specifically observed in trials of bortezomib versus no bortezomib with the same background therapy (moderate-quality evidence, prolonged OS: four studies, 1586 patients; Peto OR 0.77, 95% CI 0.65 to 0.92; moderate-quality evidence, prolonged PFS: five studies, 1855 patients; Peto OR 0.65, 95% CI 0.57 to 0.74) and in trials of bortezomib versus no bortezomib with different background therapy in each arm or compared to other agent/s (high-quality evidence, prolonged OS: five studies, 2532 patients; Peto OR 0.76, 95% CI 0.67 to 0.88; low-quality evidence, prolonged PFS: four studies, 2489 patients; Peto OR 0.67, 95% CI 0.61 to 0.75).[23]

In the latest National Comprehensive Cancer Network (NCCN) guidelines,[2,19] bortezomib-based therapy is currently the preferred regimen for transplant candidates as well as non-transplant candidates. On the other hand, for non-transplant candidates, bortezomib is the alternative option after lenalidomide for maintenance therapy. The drug is also part of the preferred regimen for patients previously treated for multiple myeloma.

While the overall safety and effectiveness of bortezomib have already been established by several studies, the disease characteristics of myeloma might predispose certain patients to thrombocytopenia and peripheral neuropathy – and the drug can exacerbate these symptoms. In addition, considering

cost-effectiveness in the Philippine setting, indefinite therapy especially for bortezomib-triplet combination regimens is highly expensive and catastrophic for patients from the lower socioeconomic classes. Overall, medical practitioners must be prudent in considering the optimal treatment and management plan offered to patients.

Nonetheless, based from clinicians' presentations and patient stories shared during the forum, there is reason to consider the substantial impact of bortezomib (Velcade ®) in the treatment and management of myeloma. From renal problems to use in autologous stem cell transplantation, it is evident that bortezomib has significantly contributed to improved clinical outcomes and consequently, better quality of life of these patients despite their differing clinical presentations. Already in its 12 years in the Philippines, bortezomib is expected to remain significant in the clinical armament against multiple myeloma.

CONCLUSION

As multiple myeloma is a highly heterogeneous molecular disease, approaches and provision of care will need to be individualized for each patient. As of this time, considering the improved outcomes, bortezomib is likely to continue being an important part of the clinical treatment and management of Filipino patients with myeloma.

REFERENCES

1. Kyle RA, Gertz MA, Witzig TE, Lust JA, Lacy MQ, Dispenzieri A et al. Review of 1027 patients with newly diagnosed multiple myeloma. Mayo Clin Proc 2003;78:21-33

2. Kumar SK, Callander NS, Alsina M, Atanackovic D, Biermann JS, Chandler JC et al. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology: Multiple myeloma Version 3.2017. *J Natl Compr Canc Netw 2017;15(2):230-269*

3. Munshi NC, Longo DL, Anderson KC. In Longo DL [Ed.] Harrison's Hematology and Oncology. New York: The McGraw-Hill Companies, Inc.;c2010. Chapter 16, Plasma cell disorders; p.205-216.

4. Huston A, Roodman GD. In Anderson KC, Ghobrial I [Eds.]. Multiple myeloma: Translational/ emerging therapies. New York: Informa Health Care USA, Inc; c2008. Myeloma bone disease; p.45-60.

5. Durie BGM. In Berenson JR [Ed.] Biology and management of multiple myeloma. New Jersey: Humana Press; c2004. Epidemiology of multiple myeloma and related disease; p.13-35.

6. Herrington LJ, Weiss NS, Olshan AD: In Schottenfeld D, Fraumerni JF Jr [Eds.]. Cancer Epidemiology and Prevention. 2nd ed. New York, NY: Oxford University Press; c1996. Multiple myeloma; p.946–970.

7. Laudico AV, Mirasol-Lumague MR, Medina V, Mapua CA, Valenzuela FG, Pukkala E. 2015 Philippine Cancer Facts and Estimates. Manila: Philippine Cancer Society; 2015.

8. Baylon HG, Tolentino JC. Velcade® safety and effectiveness study: a case series of seven Filipino adult patients diagnosed with relapsed or refractory multiple myeloma. Acta Med Philipp 2014;28(1):73-77.

9. Sonneveld P, De Wit E, Moreau P. How have evolutions in strategies for the treatment of relapsed/refractory multiple myeloma translated into improved outcomes for patients? Crit Rev Oncol Hematol 2017;112:153-170. doi:10.1016/ j.critrevonc.2017.02.007

10. Joshua D, Brown R, Ho PJ. In Brown R, Ho PJ [Eds]. Multiple myeloma: methods and protocols. New Jersey: Humana Press; c2005. Multiple myeloma: challenges and opportunities; p.1-4.

11. Fonseca R, Bersagel PL. In Rajkumar SV, Kyle RA. [Eds.] Treatment of multiple myeloma and related disorders. New York: Cambridge University Press; c2009. Diagnosis and genetic classification of multiple myeloma; p.1-17.

12. Hideshima T, Raje N. In Anderson KC, Ghobrial I [Eds.].Multiple myeloma: Translational/emerging therapies. New York: Informa Health Care USA, Inc; c2008. The role of the bone marrow microenvironment in the pathogenesis of multiple myeloma; p.23-44.

13. Kumar SK, Rajkumar SV, Dispenzieri, Lacy MQ, Hayman SR, Buadi FK et al. Improved survival in multiple myeloma and the impact of novel therapies. Blood 2008;111(5):2516-2520.

14. Kumar S, Vij R, Noga SJ, Berg D, Brent L, Dollar L et al. Treating multiple myeloma with oral therapies. Clin Lymphoma Myeloma Leuk 2017. doi:10.1016/j.clml.2017.02.024.

15. Kumar SK, Dispenzieri A, Lacy MQ et al. Continued improvement in survival in multiple myeloma: changes in early mortality and outcomes in older patients. Leukemia 2014; 28:1122-1128.

16. Kumar S. Progress in the treatment of multiple myeloma. Lancet. 2006;367:791-792.

17. Lonial S, Nooka AK. Myeloma is not a single disease. J Oncol Pract 2016;12:287–92

18. Ludwig H, Deforge M. Multiple myeloma: new treatments gain momentum. Lancet 2016; published online Dec 16. doi:10.1016/S0140-6736 (16)32405-9

19. Kumar SK, Callander NS, Alsina M, Atanackovic D, Biermann JS, Castillo J et al. National Comprehensive Cancer Network (NCCN) Guidelines Insights: Multiple Myeloma, Version 3.2018 Featured Updates to the NCCN Guidelines. J Natl Compr Canc Netw 2018;16(1):11-20 doi: 10.6004/jnccn.2018.0002

20. Boccadoro M, Morgan G, Cavenagh J. Preclinical evaluation of the proteasome inhibitor bortezomib in cancer therapy. Cancer Cell Int 2005, 5:18 doi:10.1186/1475-2867-5-18

21. Field-Smith A, Morgan GJ, Davies FE. Bortezomib (Velcade ™) in the treatment of multiple myeloma. Ther Clin Risk Manag 2006:2(3)271-279.

22. Moreau P, Richardson PG, Cavo M. Proteasome inhibitors in multiple myeloma: 10 years later. Blood 2012;120(5):947–59.

23. Scott K, Hayden PJ, Will A, Wheatley K, Coyne I. Bortezomib for the treatment of multiple myeloma. Cochrane Database Syst Rev 2016:4 (CD010816). doi:10.1002/ 14651858. CD010816. pub2.