The risk factors for herpes zoster in bortezomib treatment in patients with multiple myeloma

Yang-Seon Yi¹, Joo-Seop Chung¹, Moo-Kon Song¹, Ho-Jin Shin¹, Young-Mi Seol¹, Young-Jin Choi¹, Goon-Jae Cho¹, Gyeong-Won Lee², Joon-Ho Moon³, In-Hye Hwang¹, Kang-Hee Ahn¹, Hee-Sun Lee¹, Kyung-Hwa Shin⁵, Jong-Min Hwang¹

Department of Hematology-Oncology, ¹Busan Cancer Center, Pusan National University Hospital Medical Research Institute, Busan, ²School of Medicine, Gyeongsang National University Hospital, Jinju, ³Kyungpook National University Hospital, Kyungpook National University School of Medicine, Daegu, Korea

Background
Bortezomib has significant activity in treating multiple myeloma (MM). The risk of herpes zoster (HZ) has been reported to increase significantly with bortezomib treatment, but the predisposing factors for HZ are not clear. This study is a retrospective analysis of the relevant risk factors for HZ in Korean MM patients treated with bortezomib.

Methods
Sixty-six patients with refractory or relapsed MM who underwent chemotherapy with bortezomib were included in the study. Prophylactic antiviral drugs were not used for treatment. The following parameters were reviewed: age, gender, stage and type of MM, extent of previous treatment, history of HZ, duration from the time of diagnosis to the time of bortezomib treatment initiation, and absolute lymphocyte counts (ALC) at the time of bortezomib treatment initiation.

Results
The incidence of HZ was 16.7%. There were no intergroup differences between the HZ-positive and the HZ-negative groups with regard to a history of HZ, number of previous treatments, and exposure to steroids before bortezomib treatment. The median duration from the time of MM diagnosis to the time of bortezomib treatment initiation in the HZ-positive group was significantly shorter than that in the HZ-negative group. The median ALC at the time of bortezomib initiation in the HZ-positive group was significantly lower than that in the HZ-negative group.

Conclusion
Bortezomib itself might act as a risk factor for HZ by inhibiting cell-mediated immunity, and patients with low ALC at the time of bortezomib treatment initiation were at greater risk of HZ during bortezomib treatment.

Key Words Multiple myeloma, Protease inhibitors, Herpes zoster

INTRODUCTION

Multiple myeloma (MM) is characterized by the malignant proliferation of a plasma cell originating from a single clone and is associated with innate impairment of humoral immunity rather than cell-mediated immunity. In addition, in patients with MM, treatment-associated immunodeficiency increases the susceptibility to various infections.

Bortezomib, introduced in the late 1990s, has significant activity against MM and is one of the most widely used drugs in the treatment of MM. As a proteosome inhibitor, bortezomib directly induces apoptosis of myeloma cells and acts in the bone marrow microenvironment, inhibits myeloma cells binding to bone marrow stromal cells, alters cytokine secretion, and restricts angiogenesis [1-3]. Notably, the risk of HZ was significantly higher in patients treated with bortezomib. In the Assessment of Proteosome Inhibition for Extending Remissions APEX study, the incidence of HZ after bortezomib treatment was significantly higher than that after...
Risk factors for herpes zoster in bortezomib in MM

Table 1. Comparison of patient characteristics between HZ-positive group and HZ-negative group at the time of diagnosis of multiple myeloma.

| Clinical and laboratory characteristics | HZ-positive group (N=12) | HZ-negative group (N=54) | P |
|----------------------------------------|--------------------------|--------------------------|---|
| At the time of diagnosis               |                          |                          |   |
| Median age, years (range)              | 61.5 (40-76)             | 63.5 (44-78)             | 0.549 |
| Sex, N (%)                             |                          |                          | 0.295 |
| Male                                   | 8 (66.7)                 | 27 (50)                  |   |
| Female                                 | 4 (33.3)                 | 27 (50)                  |   |
| ECOG, N (%)                            |                          |                          | 0.426 |
| 0/1                                    | 10 (83.3)                | 39 (72.2)                |   |
| 2/3                                    | 2 (16.7)                 | 15 (27.8)                |   |
| Type of myeloma, N (%)                 |                          |                          | 0.457 |
| IgG                                    | 5 (41.7)                 | 30 (55.6)                |   |
| IgA                                    | 3 (25.0)                 | 13 (24.1)                |   |
| IgM                                    | 0 (0)                    | 1 (1.8)                  |   |
| IgD                                    | 0 (0)                    | 1 (1.8)                  |   |
| Light chain                            | 4 (33.3)                 | 6 (11.1)                 |   |
| Nonsecretory                           | 0 (0)                    | 0 (0)                    |   |
| Unknown                                | 0 (0)                    | 3 (5.6)                  | 0.060 |
| International staging system, N (%)    |                          |                          |   |
| I                                      | 2 (16.7)                 | 4 (7.4)                  |   |
| II                                     | 1 (8.3)                  | 24 (44.4)                |   |
| III                                    | 9 (75.0)                 | 26 (48.1)                |   |
| Laboratory findings                    |                          |                          |   |
| Median serum M protein (range), g/dL   | 5 (3.03-9.09)            | 4.5 (0.23-9.81)          | 0.214 |
| Median β2MG (range), μg/mL             | 6.5 (3.28-15.83)         | 5.0 (1.75-39.3)          | 0.572 |
| Median serum albumin (range), g/dL     | 3.5 (2.4-4.6)            | 3.0 (1.6-4.8)            | 0.073 |
| Median serum creatinine (range), mg/dL  | 1.5 (0.6-2.6)            | 1.0 (0.5-9.0)            | 0.577 |
| Median Hb (range), g/dL                | 8.5 (7.8-12.9)           | 9.0 (5.3-14.9)           | 0.888 |

Abbreviations: HZ, herpes zoster; ECOG, eastern cooperative oncology group; β2MG, β2-microglobulin.
RESULTS

1. HZ incidence and characteristics during bortezomib treatment

The incidence of HZ during bortezomib treatment was 16.7% (12/66 patients). The median duration from bortezomib treatment initiation to HZ onset was 2 months (range, 1-13 months). In 1 patient, HZ took longer than 6 months to develop (13 months), whereas in the remaining 11 patients, HZ developed within 6 months of the initial bortezomib administration. The patient with the 13-month interval time received 10 cycles of bortezomib in combination with dexamethasone for 28 months until disease progression developed. Nine of the 12 patients (75%) resumed bortezomib after receiving HZ treatment. The remaining 3 patients (25%) discontinued bortezomib treatment for reasons of disease progression, self-refusal, and poor PS, respectively.

2. Patient characteristics at MM diagnosis

The median age, gender, ECOG PS, disease type, and stage of disease did not account for significant differences between the HZ-positive and HZ-negative groups (Table 1). Laboratory parameters such as the median serum M protein, β2-microglobulin, albumin, creatinine, and Hb were similar between the 2 groups.

3. Patient characteristics at bortezomib treatment initiation

A history of HZ prior to bortezomib treatment in the HZ-positive group occurred no more frequently than in the HZ-negative group (8.3% vs. 14.9%, P=0.554) (Table 2). Thus, a history of HZ at the initiation of bortezomib treatment may have no influence on HZ occurrence during bortezomib treatment.

Although all patients previously received more than 1 treatment, the number of treatments prior to bortezomib initiation did not significantly associate with HZ incidence (P=0.119). The rate of steroid exposure did not differ significantly between the two groups. However, in the HZ-positive group, the median duration from MM diagnosis to the initiation of bortezomib treatment was significantly shorter when compared to the HZ-negative group (10.5 vs. 24 months, P=0.002) (Fig. 1).

No significant differences were detected in laboratory parameters (e.g., serum M protein level, β2-microglobulin, albumin, creatinine, Hb, and ANC) at the initiation of bortezomib regimen.

| Table 2. Comparison of patient characteristics between HZ-positive group and HZ-negative group at the initiation of bortezomib treatment. |
|---------------------------------------------------------------|
| Clinical and laboratory characteristics | HZ-positive group (N=12) | HZ-negative group (N=54) | P |
|-------------------------------------------|--------------------------|--------------------------|---|
| At the time of initiation of bortezomib treatment | | | |
| HZ history, N (%) | | | |
| Present | 1 (8.3) | 8 (14.9) | 0.554 |
| Absent | 11 (91.7) | 46 (85.1) | |
| Prior treatment, N (%) | | | |
| 0 | 0 (0) | 0 (0) | 0.666 |
| 1 | 6 (50.0) | 25 (46.3) | |
| 2 | 3 (25.0) | 20 (37.0) | |
| ≥ 3 | 3 (25.0) | 9 (16.7) | |
| Prior treatment with steroids, N (%) | | | |
| Present | 12 (100.0) | 51 (94.4) | 0.403 |
| Absent | 0 (0) | 3 (5.6) | |
| Median duration from the time of diagnosis to the time of bortezomib initiation, months (range) | 10.5 (2-36) | 24 (2-98) | 0.002 |
| Laboratory findings | | | |
| Median serum M protein (range), g/dL | 3.0 (0.48-9.64) | 2.5 (0.10-9.63) | 0.849 |
| Median β2MG (range), μg/mL | 7.0 (3.15-20.0) | 4.0 (1.86-20.0) | 0.128 |
| Median serum albumin (range), g/dL | 3.5 (2.0-4.7) | 3.5 (1.3-5.0) | 0.479 |
| Median serum creatinine (range), mg/dL | 1.5 (0.6-5.2) | 1.0 (0.5-6.8) | 0.144 |
| Median Hb (range), g/dL | 8.5 (4.9-11.9) | 10.0 (7.1-15.8) | 0.071 |
| Median ANC (range), ×10^9/L | 3.5 (0.98-7.04) | 2.5 (0.45-9.35) | 0.258 |
| Median ALC (range), ×10^9/L | 1.0 (0.43-1.50) | 1.5 (0.27-3.20) | 0.018 |
| Bortezomib regimen, n (%) | | | |
| Bortezomib | 1 (8.3) | 5 (9.3) | 0.119 |
| Bortezomib/dexamethasone | 6 (50.0) | 38 (70.4) | |
| Bortezomib/doxorubicin/dexamethasone | 0 (0) | 3 (5.6) | |
| Bortezomib/cyclophosphamide/dexamethasone | 2 (16.7) | 6 (11.1) | |
| Bortezomib/cyclophosphamide/thalidomide/dexamethasone | 2 (16.7) | 2 (3.7) | |
| Bortezomib/thalidomide/dexamethasone | 1 (8.3) | 0 (0) | |
| Bortezomib regimen with Dexamethasone, N (%) | | | 0.920 |
| Present | 11 (91.7) | 49 (90.7) | |
| Absent | 1 (8.3) | 5 (9.3) | |

Abbreviations: HZ, herpes zoster; β2MG, β2-microglobulin.
Risk factors for herpes zoster in bortezomib in MM

In both groups, more than half of the patients were given bortezomib in combination with dexamethasone. Neither dexamethasone nor other drugs used in combination with bortezomib were significantly associated with HZ occurrence during treatment.

**DISCUSSION**

HZ commonly occurs in elderly and immunocompromised individuals, and is associated with decreased cell-mediated immunity [12]. In immunocompromised individuals, particularly in those with impaired cell-mediated immunity, HZ can disseminate and cause more serious organ involvement, including hepatitis, pneumonia, and encephalitis [12]. However, impaired innate immunity in myeloma primarily affects humoral immunity rather than cell-mediated immunity; therefore, patients with MM were not at increased risk for HZ [13].

Bortezomib is one of the most widely used drugs for treating MM, and it is effective as one of the first-line regimen in previously untreated myeloma patients [7] as well as the second-line regimen in relapsed or refractory patients [14-16].

Several studies have indicated increased HZ risk during bortezomib treatment. In a phase III APEX trial, the incidence of HZ significantly increased in the bortezomib group compared to the high-dose dexamethasone group in relapsed MM patients [4]. Other studies identified an association between bortezomib and increased HZ incidence in the range of 10-22.3% in relapsed MM [6, 8, 10, 11]. The overall HZ incidence in the present study was 16.7% in patients with refractory or relapsed MM, which is comparable to previous studies.

In addition to myeloma-related immunodeficiency and its complications, cumulative immunosuppression by salvage therapy may also increase susceptibility to infection. However, the present study showed a significantly shorter duration from MM diagnosis to bortezomib treatment initiation in the HZ-positive group compared to the HZ-negative group, identical to data reported in the previous study [8], suggesting that disease duration is not a risk factor for zoster development. This result is supported by several recent studies on bortezomib-associated HZ in newly diagnosed myeloma patients. The incidence of HZ during bortezomib treatment in newly diagnosed patients is similar to HZ incidence in relapsed or refractory cases, in the range of 13-20% [5, 7, 9, 17].

Several experimental studies have shown that bortezomib decreases the number and function of CD56+ NK cells and CD8+ cytotoxic T cells, with no definite decrease in CD4+ T cells [18], and it inhibits the function of dendritic cells [19]. Bortezomib targets the 26S proteasome and thereby prevents the activation of nuclear factor (NF)-κB, which then leads to inhibition of T cell activation as well as anti-myeloma effects [20]. Although mechanisms are not clear, this may lead to impaired cell-mediated immunity such as above. Thus, the use of bortezomib might itself act as a predisposing factor to HZ. In the present study, the median ALC at bortezomib treatment initiation in the HZ-positive group was significantly lower than in the HZ-negative group (P=0.018).

![Fig. 1. Median duration from the time of diagnosis to the time of bortezomib treatment initiation (months) in the herpes zoster-positive and herpes zoster-negative groups. The interval between the time of diagnosis and the time of bortezomib treatment initiation in the herpes zoster-positive group was significantly shorter than that in the herpes zoster-negative group (P=0.002).](image1)

![Fig. 2. Median ALC at the time of bortezomib treatment initiation in the herpes zoster-positive and herpes zoster-negative groups. The median absolute lymphocyte counts (ALC) at the time of bortezomib initiation in the herpes zoster-positive group was significantly lower than that in the herpes zoster-negative group (P=0.018).](image2)
Although untreated MM patients were not at increased risk for HZ [13], HZ was more likely to occur following dexamethasone-based regimens due to decreased cell-mediated immunity [17]. However, as shown in the phase III APEX trial, the incidence of HZ was significantly higher in the bortezomib group despite the comparable ALC baseline levels detected in bortezomib-treated patients with HZ and dexamethasone-treated patients with HZ [4]. The incidence of Candida and other fungal infections was significantly higher in the dexamethasone group, and the overall incidence of infection was similar between the two groups [4]. These results suggest that bortezomib and dexamethasone have different immunosuppressive properties, and the associated HZ development may involve more than the degree of lymphocytopenia.

In conclusion, the use of bortezomib itself is a risk factor for HZ because it inhibits T cell activation and impairs cell-mediated immunity. Clinically, patients who presented decreased ALC at the initiation of bortezomib treatment were associated with HZ development. Future studies will focus on serial changes of the specific lymphocyte subsets and other immune cells that affect zoster development, and on the strategy of prophylaxis.

REFERENCES

1. Curran MP, McKeage K. Bortezomib: a review of its use in patients with multiple myeloma. Drugs 2009;69:859-88.
2. Hideshima T, Richardson P, Chauhan D, et al. The proteasome inhibitor PS-341 inhibits growth, induces apoptosis, and overcomes drug resistance in human multiple myeloma cells. Cancer Res 2001;61:3071-6.
3. Richardson PG, Hideshima T, Anderson KC. Bortezomib (PS-341): a novel, first-in-class proteasome inhibitor for the treatment of multiple myeloma and other cancers. Cancer Control 2003;10:361-9.
4. Chanan-Khan A, Sonneveld P, Schuster MW, et al. Analysis of herpes zoster events among bortezomib-treated patients in the phase III APEX study. J Clin Oncol 2008;26:4784-90.
5. Mateos MV, Hernández JM, Hernández MT, et al. Bortezomib plus melphalan and prednisone in elderly untreated patients with multiple myeloma: results of a multicenter phase 1/2 study. Blood 2006;108:2165-72.
6. Palumbo A, Ambrosini MT, Benevolo G, et al. Bortezomib, melphalan, prednisone, and thalidomide for relapsed multiple myeloma. Blood 2007;109:2767-72.
7. San Miguel JF, Schlag R, Khugueva NK, et al. Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. N Engl J Med 2008;359:906-17.
8. Kim SJ, Kim K, Kim BS, et al. Bortezomib and the increased incidence of herpes zoster in patients with multiple myeloma. Clin Lymphoma Myeloma 2008;8:237-40.
9. Zheng W, Wei G, Ye X, et al. Bortezomib in combination with dexamethasone and subsequent thalidomide for newly-diagnosed multiple myeloma: a Chinese experience. Leuk Res 2009;33:1615-8.
10. Ohguchi H, Sugawara T, Ishikawa I, et al. A retrospective analysis of bortezomib therapy for Japanese patients with relapsed or refractory multiple myeloma: beta2-microglobulin associated with time to progression. Int J Hematol 2009;89:342-7.
11. Palumbo A, Gay F, Bringhen S, et al. Bortezomib, doxorubicin and dexamethasone in advanced multiple myeloma. Ann Oncol 2008;19:1160-5.
12. Gershon AA, Gershon MD, Breuer J, Levin MJ, Oaklander AL, Griffiths PD. Advances in the understanding of the pathogenesis and epidemiology of herpes zoster. J Clin Virol 2010;48(Suppl 1):S2-7.
13. Morison WL. Letter: herpes simplex and herpes zoster in neoplasia. Lancet 1974;1:1293.
14. 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.
15. 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.
16. Richardson PG, Barlogie B, Berenson J, et al. phase 2 study of bortezomib in relapsed, refractory myeloma. N Engl J Med 2003;348:2609-17.
17. Nucci M, Anaissie E. Infections in patients with multiple myeloma in the era of high-dose therapy and novel agents. Clin Infect Dis 2009;49:1211-25.
18. Uy GL, Peles S, Fisher NM, Tomasson MH, DiPersio JF, Vrij R. Bortezomib prior to autologous transplant in multiple myeloma: effects on mobilization, engraftment, and markers of immune function. Biol Blood Marrow Transplant 2006;12(Suppl 1):116.
19. Nencioni A, Garuti A, Schwarzenberg K, et al. Proteasome inhibitor-induced apoptosis in human monocyte-derived dendritic cells. Eur J Immunol 2006;36:681-9.
20. Matsumoto M, Yamada T, Yoshinaga SK, et al. Essential role of NF-kappa B-inducing kinase in T cell activation through the TCR/CD3 pathway. J Immunol 2002;169:1151-8.