# Acyclovir Prophylaxis Against Varicella Zoster Virus Reactivation in Multiple Myeloma Patients Treated With Bortezomib-Based Therapies: A Retrospective Analysis of 100 Patients

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Immunocompromised patients, such as those receiving systemic corticosteroids, chemotherapy, or immunosuppressive drugs following transplant, are at increased risk of developing herpes zoster.[1] Development of herpes zoster results from reactivation of latent varicella zoster virus (VZV), present in the dorsal root and cranial nerve ganglia following resolution of varicella (chickenpox).[1,2] It is associated with a painful rash that usually subsides within 2-4 weeks but can also be associated with clinically important sequelae; for example, 9%-34% of patients with herpes zoster develop postherpetic neuralgia, which can be associated with persistent or recurrent pain lasting for months or years.[2,3]

In immunocompetent individuals, cell-mediated immunity (CMI) is thought to be primarily responsible for prevention of VZV reactivation.[4] Thus, patients with hematologic malignancies

## ABSTRACT

**Background:** Previous studies have indicated that, in patients with multiple myeloma (MM), bortezomib is associated with an increased incidence of herpes zoster, resulting from reactivation of latent varicella zoster virus (VZV).

**Objective:** Our objective was to determine whether increased risk of VZV reactivation could be abrogated by using prophylactic acyclovir.

**Methods:** We retrospectively evaluated 100 consecutive MM patients treated with bortezomib-based therapies at the Roswell Park Cancer Institute for development of herpes zoster. Frontline and relapsed/refractory patients were included, and patients received bortezomib alone or in combination with agents such as doxorubicin, melphalan, or dexamethasone. All patients received >4 weeks of acyclovir prophylaxis (400 mg twice daily), which was initiated prior to starting treatment with bortezomib and discontinued 4 weeks following bortezomib.

**Results:** Median patient age was 62 years, 57% were male, and most (56%) had Durie-Salmon stage IIIA MM. None of the 100 MM patients receiving acyclovir prophylaxis developed herpes zoster during treatment with bortezomib, irrespective of patients receiving a wide variety of concomitant antimyeloma therapies and regardless of response to bortezomib-based therapy. One additional patient, found to be noncompliant with acyclovir therapy, experienced VZV reactivation, having received 3 cycles of bortezomib (3 weeks each cycle) in combination with cyclophosphamide and dexamethasone.

**Limitations:** Limitations of the study include its small size and retrospective nature.

**Conclusions:** The increased risk of VZV reactivation observed in previous studies of bortezomib-based therapy was completely abrogated in this series of patients who received prophylaxis with acyclovir.

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such as lymphoma and leukemia, which directly impact white blood cells and thus a patient's ability to mount an effective immune response, have an increased risk of developing herpes zoster.[5] As multiple myeloma (MM) is characterized by proliferation of malignant plasma cells, the immunosuppression observed in MM is thought to be chiefly associated with defects in humoral immunity rather than CMI.[6] It has also been shown that both CMI and humoral immunity are compromised in untreated MM patients.[7] Furthermore, the innate immunodeficiency associated with MM as well as the myelosuppressive effects associated with the use of melphalan and other conventional and novel agents give rise to infections and represent a significant cause of morbidity and mortality in MM patients.[8,9]

Of particular interest, an increased incidence of herpes zoster has been reported in patients with MM during treatment with the proteasome inhibitor bortezomib.[10-15] In the phase 3 Assessment of Proteasome Inhibition for Extending Remissions (APEX) study of single-agent bortezomib versus high-dose dexamethasone in relapsed MM patients following one or more prior lines of therapy, 13% of patients in the bortezomib arm reported herpes zoster versus 5% in the dexamethasone arm ($P < .001$);[10] routine use of anti-infective prophylaxis was not mandated in this study. Similarly, in patients not receiving acyclovir prophylaxis in the phase 3 Velcade as Initial Standard Therapy in Multiple Myeloma (VISTA) trial of bortezomib plus melphalan–prednisone (VMP) versus melphalan–prednisone (MP) alone in previously untreated MM patients ineligible for transplantation, 13% in the VMP arm developed herpes zoster compared with 4% in the MP arm.[13] A retrospective analysis by Kim et al.[12] also showed that the rate of herpes zoster increased from 11% at baseline to 22.3% during treatment with bortezomib. These results for bortezomib-treated patients are in contrast to those seen in studies of other anti-MM treatments, such as MP with or without thalidomide, in which the frequency of herpes zoster during treatment was reported to be 1%–3%.[16,17]

In line with these data, current guidelines for the treatment of MM state that herpes zoster prophylaxis should be considered in patients receiving bortezomib,[18] and it has been standard practice to administer concurrent acyclovir in patients treated with bortezomib at the Roswell Park Cancer Institute for several years. The aim of this retrospective analysis was to evaluate the efficacy of acyclovir prophylaxis in preventing VZV reactivation in a population of MM patients who were treated with bortezomib at our center. The population included both treatment-naive and relapsed/refractory patients, and most patients received bortezomib as part of combination regimens.

## METHODS

This retrospective analysis included consecutive MM patients treated with bortezomib-based therapies at the Roswell Park Cancer Institute (Buffalo, NY) between January 2001 and June 2009. All patients received bortezomib at doses of 1.0 or 1.3 mg/m$^2$, although duration of therapy and treatment regimens varied. Patients received bortezomib either alone or in combination with other agents. In addition to bortezomib-based anti-MM therapy, all patients received >4 weeks of prophylactic acyclovir; only those patients compliant with acyclovir are considered in this analysis. Acyclovir was initiated prior to starting treatment with bortezomib and was discontinued 4 weeks after the last dose of bortezomib therapy. The dose of acyclovir was fixed at 400 mg twice daily, irrespective of renal function, with the exception of one patient who received 800 mg once daily.

Compliance with acyclovir was evaluated through review of patient medical records. Response to therapy was assessed using the European Group for Blood and Marrow Transplantation criteria,[19] and patients were monitored throughout treatment for adverse events, including VZV reactivation. Blood samples for determination of absolute lymphocyte count (ALC) and absolute neutrophil count (ANC) were routinely obtained before starting bortezomib therapy and after the end of the last cycle. Summary statistics are used to describe the patient population evaluated here.

## RESULTS

In total, 100 patients are described in this series. One additional patient who was found to be noncompliant with the prescribed acyclovir therapy was also followed, and this case is discussed separately (see below, Patient with Reactivation of VZV).

Patient and disease characteristics at initiation of therapy are outlined in Table 1. A total of 59 (59%) patients received bortezomib-based therapy as their frontline regimen, and 41 patients had relapsed/refractory MM. Of these 100 patients, 87 received bortezomib as part of a combination regimen and 13 received single-agent bortezomib. The majority of patients (65%) received bortezomib as part of a doxorubicin-based regimen; among patients receiving frontline bortezomib-based therapy, the most common regimen was bortezomib, thalidomide, and doxorubicin (71% [n = 42] of frontline patients). In total, 16 patients had prior stem-cell transplant. Median ALC and ANC values at initiation of therapy were $1.46 \times 10^9$/L and $2.995 \times 10^9$/L, respectively.

Of the 100 patients who received bortezomib-based therapy and antiviral prophylaxis, none experienced VZV reactivation. This effect was observed despite the heterogeneous patient population. Acyclovir was effective in preventing VZV reactivation regardless of response to bortezomib-based therapy—in patients with relapsed/refractory MM, the overall response rate (partial response or better, ORR) was 46% (n = 19), while in patients receiving bortezomib-based frontline therapy, the ORR was 61% (n = 36). The use of bortezomib in a wide variety of combination regimens with different chemotherapeutic agents did not affect the efficacy of acyclovir. Equally, whether patients received bortezomib as frontline therapy or in the relapsed setting did not affect the risk of VZV reactivation. Of particular note, median ALC and ANC values decreased slightly during treatment (Table 1).

**Table 1**

Patient and Disease Characteristics and Treatment Regimens

| BASELINE CHARACTERISTIC, NO. (%) | PATIENTS (N = 100) |
|---|---|
| Median age, years (range) | 62 (40–86) |
| Male | 57 (57) |
| Race/ethnicity | |
| White | 91 (91) |
| Black | 7 (7) |
| Hispanic | 2 (2) |
| DSS stage | |
| IA | 14 (14) |
| IIA | 12 (12) |
| IIIA | 56 (56) |
| IIIB | 18 (18) |
| Previous herpes zoster infection | 10 (10) |
| Hematologic parameters at baseline, median (range) | |
| ALC ($\times 10^9$/L) | 1.46 (0.1–5.88)[b] |
| *ALC posttreatment* | 0.93 (0.11–5.97)[b] |
| ANC ($\times 10^9$/L) | 2.995 (1.01–17.15) |
| *ANC posttreatment* | 2.85 (0.8–15.7) |
| CRP (mg/L) | 2.7 (0.2–96.9)[c] |
| $\beta_2$-microglobulin (mg/L) | 3.29 (1.21–15.3)[b] |
| Hemoglobin | 11.2 (5.7–15.4) |
| Platelets | 208,500 (26,000–483,000) |
| Creatinine | 1.1 (0.6–7.3) |
| Treatment, no. (%) | |
| Prior treatment | |
| Relapsed/refractory | 41 (41) |
| Frontline | 59 (59) |
| Stem-cell transplant | 16 (16) |
| Therapy received in present analysis | |
| Bortezomib alone | 13 (13) |
| Bortezomib plus melphalan-based regimen[d] | 6[a] (6) |
| Bortezomib plus doxorubicin-based regimen[e] | 65[a] (65) |
| Bortezomib plus dexamethasone-based regimen[f] | 15 (15) |
| Bortezomib plus other agents[g] | 3 (3) |
| Median number of cycles (range) | 6 (1–19) |
| Median duration of therapy (months) (range) | 5 (1–14) |

Abbreviations: ALC, absolute lymphocyte count; ANC, absolute neutrophil count; CRP, C-reactive protein; DSS, Durie-Salmon stage.

[a] Includes one patient also receiving dexamethasone, thus N = 102 as two patients are counted twice.

[b] Data missing for one patient.

[c] Data missing for two patients.

[d] Bortezomib (btz)+melphalan (mel), btz+mel+prednisone, btz+mel+dexamethasone (dex)+lenalidomide (len).

[e] Btz+doxorubicin (dox), btz+dox+len, btz+dox+thalidomide (thal), btz+dox+thal+cytoxan, btz+dox+dex+thal.

[f] Btz+dex, btz+dex+thal, btz+dex+len, btz+dex+cytoxan, btz+dox+dex+thal.

[g] Btz+17AA, btz+anti-trail.

### Patient with Reactivation of VCV

One additional patient with stage IIIB MM, who was found to be noncompliant with the prescribed acyclovir therapy, reported VZV reactivation during treatment with bortezomib. This patient received 3 cycles (3 weeks per cycle) of therapy with bortezomib, cyclophosphamide, and dexamethasone. She was prescribed acyclovir 200 mg twice daily but did not initiate the therapy.

## DISCUSSION

In this series of 100 patients treated with bortezomib and prophylactic acyclovir, no patients experienced VZV reactivation. Compared with patients who received bortezomib without prophylaxis in other studies.[10,13] Our data suggest that this side effect of bortezomib therapy can be easily prevented. Effective prophylaxis was observed despite the potential immunosuppressive effects of either previous chemotherapy in relapsed/refractory patients or concomitant chemotherapeutic agents administered as part of a combination regimen in both frontline and relapsed/refractory patients.[7] The slight decrease in ALC and ANC levels observed from baseline may have been indicative of increased immunosuppression. Although this would have increased the possibility for VZV reactivation, acyclovir prophylaxis appeared to prevent such. Furthermore, a previous analysis of the APEX trial indicated that patients who developed herpes zoster tended to have below-normal ALC counts, an effect that was more pronounced in the bortezomib arm than in dexamethasone-treated patients.[10]

These results are supported by previous studies suggesting that prophylactic use of antiviral agents in patients receiving bortezomib prevents herpes zoster.[20-24] For example, in a study of 98 patients with relapsed MM who were initially scheduled to receive bortezomib without antiviral prophylaxis, 4 of the first 11 patients developed herpes zoster.[20] Prophylactic acyclovir (400 mg 3 times daily) was administered to 32 subsequent patients and no cases of VZV reactivation were reported in this group. Furthermore, another 55 patients in this study received a decreased acyclovir dose of 400 mg once daily, with no further cases of VZV reactivation reported.[20] In the phase 3 VISTA trial of previously untreated MM patients, although 13% of patients in the VMP arm initially developed herpes zoster, this rate was reduced to only 3% in patients who subsequently received antiviral prophylaxis.[13] Of particular note, the rate of VZV reactivation in the absence of prophylaxis with VMP in VISTA appeared similar to the rate with single-agent bortezomib in the APEX trial, supporting the hypothesis that this is a bortezomib-specific effect that is consistently seen, regardless of prior treatment status or use of concomitant agents. This is also supported by the finding in the APEX study that, although the incidence of herpes zoster was increased in the bortezomib arm, this was the only viral infection significantly elevated by bortezomib compared with high-dose dexamethasone.[10] In addition, multivariate analysis of other potential prognostic factors for herpes zoster in the APEX study did not identify any apparent

predisposing factors for VZV reactivation beyond the positive correlation observed with bortezomib treatment,[10] which further suggests that VZV reactivation is a highly specific effect of bortezomib.

The etiology of VZV reactivation in patients receiving bortezomib is poorly understood. A potential explanation may be that bortezomib acts in favor of latent VZV by directly inhibiting the immunoproteasome,[25] which is important in the suppression of latent VZV activation. Unlike other, closely related herpes viruses, VZV is thought to express transcripts during latency;[26] and as immunoproteasomes are responsible for the generation of most major histocompatibility class I molecules,[27] proteasome inhibition by bortezomib could impair this antigen-presenting activity and, thus, increase susceptibility to viral reactivation. VZV reactivation may also be more sensitive to immunoproteasome inhibition than opportunistic infections, due to the pharmacodynamics of bortezomib. Maximal inhibition of the proteasome by bortezomib is achieved shortly after administration, and then proteasome activity recovers toward baseline;[28] thus, a latent virus already in situ, such as VZV, would be more likely to be reactivated in this limited time period as the window for opportunistic infections is relatively short. Another potential explanation for VZV reactivation may stem from the observation that bortezomib is known to affect the dorsal root ganglia,[29] which is where latent VZV is known to reside.[2]

Acyclovir is widely used, and long-term exposure, for example, in patients with genital herpes simplex viral infection, is generally well tolerated.[30-32] However, antivirals can be associated with neurotoxicity and nephrotoxicity, which are particularly relevant in MM;[33] and the effects of prolonged administration in patients with MM are yet to be fully determined.

## CONCLUSION

In conclusion, the increased risk of VZV reactivation observed in previous studies of bortezomib-based therapy appears to be completely abrogated in this series of patients who received prophylaxis with acyclovir. Acyclovir prophylaxis appears warranted for patients receiving bortezomib-based therapy, and further studies would be of benefit in identifying patients most at risk of VZV reactivation.

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