JJCO Japanese Journal of Clinical Oncology

Jpn J Clin Oncol 2011;41(3)353–357
doi:10.1093/jjco/hyq194
Advance Access Publication 14 October 2010

Low-dose Acyclovir is Effective for Prevention of Herpes Zoster in Myeloma Patients Treated with Bortezomib: A Report from the Korean Multiple Myeloma Working Party (KMMWP) Retrospective Study

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Received September 2, 2010; accepted September 13, 2010

Objective: Acyclovir prophylaxis has been considered as mandatory for patients receiving bortezomib because herpes zoster is a common adverse event associated with the use of bortezomib. Although the minimal effective dose of acyclovir for prophylaxis has not yet established, the efficacy of low-dose acyclovir prophylaxis, 400 mg once daily, has been suggested.
Methods: We retrospectively reviewed the patients receiving the low-dose acyclovir which was defined as the once daily administration of acyclovir 400 or 200 mg. All patients received bortezomib-containing chemotherapy in the setting of relapsed or refractory myeloma.
Results: Eighty patients received bortezomib-containing treatment as a salvage therapy. All patients received at least one or more treatments prior to bortezomib treatment, including autologous stem cell transplantation. Sixty-one patients received 400 mg of acyclovir once daily while 19 patients received 200 mg. Although seven cases of herpes zoster were observed from 80 patients (7/80, 8.75%), two cases of herpes zoster received 400 mg during the limited period from the first to the fourth cycle, and the other five received 200 mg. Therefore, there was no herpes zoster in patients who received 400 mg of acyclovir till the last cycle of bortezomib treatment. There were no adverse events associated with the use of acyclovir prophylaxis.
Conclusions: The administration of acyclovir 400 mg once daily during the bortezomib treatment is an effective prophylaxis for herpes zoster in patients receiving bortezomib irrespective of disease state and the type of chemotherapy regimen.

Key words: bortezomib – multiple myeloma – herpes zoster – acyclovir

INTRODUCTION

Since bortezomib was introduced for the treatment of multiple myeloma, the management of bortezomib-associated adverse events has been an important issue because those adverse events could result in inadequate treatment by delaying treatment schedules or reducing the dosage. Although peripheral neuropathy is the most frequent as well as troublesome side effect of bortezomib, herpes zoster

(varicella zoster virus reactivation) is also known as being associated with the use of bortezomib. Thus, there are many evidences supporting that bortezomib is associated with a significant risk of herpes zoster (1–3). Our group also previously reported the increased incidence of herpes zoster in the era of bortezomib (22.3%, 63/282) compared with the pre-bortezomib era (11.0%, 31/282) (4). As a result, acyclovir prophylaxis was recommended for patients receiving bortezomib, usually with acyclovir 400 mg three times daily (5,6). Although this led to a decrease in the occurrence of herpes zoster, the routine use of acyclovir prophylaxis is a still issue of debate because herpes zoster is a benign disease usually well controlled with anti-viral agents, and long-term acyclovir prophylaxis may also cause severe renal and neurological toxicity (7).

Recently, low-dose acyclovir prophylaxis, 400 mg once daily was reported to be effective as same as the conventional dose, 400 mg three times daily (8). Thus, no herpes zoster was observed in patients received 400 mg once daily like patients 400 mg three times daily. The other study using 200–400 mg of acyclovir demonstrated the efficacy of low-dose acyclovir (9). These studies showed that low-dose acyclovir prophylaxis has no adverse effects and good compliance, retaining the same efficacy as the conventional dosage. Since these results were published, some Korean institutes have used this low-dose prophylaxis strategy. However, the nationwide survey regarding its efficacy has never been performed, thus the efficacy of low-dose acyclovir prophylaxis in Asian patients has never been reported. Thus, we performed a retrospective analysis to evaluate the efficacy of low-dose acyclovir to prevent herpes zoster in Korean myeloma patients receiving bortezomib.

MATERIALS AND METHODS

We reviewed the medical records of multiple myeloma patients of four hospitals which are located from Seoul to southern part of Korea (Samsung Medical Center, SMC in Seoul, Keimyung University, KUH and Daegu Catholic University Hospital, DCUH in Daegu and Chonnam National University Hwasun Hospital, CNUHH in Jeollanam-do) from January 2008 to February 2010, and then selected 80 patients who received bortezomib-containing chemotherapy as well as low-dose acyclovir as a prophylaxis for herpes zoster. The definition of low-dose acyclovir was the oral administration of 200 or 400 mg of acyclovir once daily. Bortezomib was administered at the dosage of 1.3 mg/m^2 intravenously on days 1, 4, 8 and 11 every 3 weeks. However, according to the grade of toxicity associated with bortezomib, the dosage was reduced to 1.0 and 0.75 mg/m^2 sequentially. Tumor response was evaluated using the Blade Criteria (European Group for Blood and Marrow Transplantation/International Bone Marrow Transplant registry/Autologous Blood and Marrow transplant Registry Criteria) (10). Adverse events and their severity were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0. Fisher's exact test was applied to assess the association between categorical variables. All the statistical analyses were performed using a statistical software package (SPSS, Version 10.0, Inc., Chicago, IL, USA). Statistical significance was defined as P value less than 0.05. This study was supported by the Korean Multiple Myeloma Working Party (Protocol No. KMM96) and reviewed by the Institutional Review Board of each participating institutes. The achievement of informed consent was exempted because patients' identification was not uncovered, and there was no intervention such as drug therapy in this retrospective analysis.

RESULTS

Patient Characteristics at the Time of Bortezomib Treatment

The median age of 80 patients was 61 years (range 40–83 years). Bortezomib was used alone or combined with other drugs such as dexamethasone, cyclophosphamide and thalidomide as summarized in Table 1. Co-morbidities affecting drug absorption such as gastrointestinal amyloidosis were not diagnosed in our retrospective cohort. Because the bortezomib-containing chemotherapy was used as a salvage treatment, all patients had been treated with at least one treatment regimen, including VAD (vincristine, Adriamycin, dexamethasone), TD (thalidomide, dexamethasone), TCD (thalidomide, cyclophosphamide, dexamethasone), MP (melphalan, prednisolone), CD (cyclophosphamide, dexamethasone), CP (cyclophosphamide, prednisolone) or high-dose chemotherapy followed by autologous stem cell transplantation (ASCT) before they were treated with bortezomib. The median number of previous treatment regimens prior to bortezomib treatment, including ASCT, was 1 (range 1–4). Thus, the majority of patients ($n = 48$) received the bortezomib-containing chemotherapy as a second line treatment, and the median time interval between diagnosis and bortezomib start was 8.95 months (range 1.30–77 months).

Acyclovir Prophylaxis and the Occurrence of Herpes Zoster

The cycle length of bortezomib treatment was from 3 to 4 weeks according to the type of regimen or each participating center's practice. The median number of bortezomib treatment cycle was 5 (range 2–8). Sixty-one patients received 400 mg of acyclovir once daily when they started their bortezomib treatment. Among them, the duration of acyclovir prophylaxis was different. Thus, three hospitals (SMC, KUH, DCUH) used acyclovir continuously till the end of bortezomib treatment ($n = 36$). One hospital (CNUHH) used acyclovir until the end of the fourth cycle ($n = 25$) according to the previous result showing herpes zoster mainly occurred within the first three cycles of bortezomib (4). Among these

Table 1. The characteristics of patients at the time of bortezomib treatment

Clinical and laboratory characteristics	Total	400 mg	200 mg	*P* value
Gender				
Male	38	30	8	
Female	42	31	11	0.611
Age				
<60	31	26	5	
≥60	49	35	14	0.283
ECOG PS				
0, 1	71	54	17	
2, 3	9	7	2	>0.99
Type				
IgG kappa/lambda	27/23	22/15	5/8	
IgA kappa/lambda	5/8	4/7	1/1	
IgD lambda	4	2	2	
Light chain disease	13	11	2	0.470
Stage				
II	16	13	3	
III	64	48	16	0.750
Previous zoster history				
Absence	75	56	19	
Presence	5	5	0	0.332
Previous ASCT				
No	60	46	14	
Yes	20	15	5	>0.99
Number of previous treatment				
1	48	37	11	
≥2	32	24	8	>0.99
Serum Cr				
<1.5 g/dl	66	55	11	
≥1.5 g/dl	14	6	8	0.003
Bortezomib treatment				
Bortezomib alone	1	0	1	
Vel/D	40	24	16	
PAD	3	3	0	
Vel/CD	26	23	3	
Vel/TCD	10	10	0	0.015
Herpes zoster				
None	73	59	14	
Occurrence	7	2	5	0.007

ASCT, autologous stem cell transplantation; Vel/D, bortezomib, dexamethasone; PAD, bortezomib, doxorubicin, dexamethasone; Vel/CD, bortezomib, cyclophosphamide, dexamethasone; Vel/TCD, bortezomib, thalidomide, cyclophosphamide, dexamethasone.

61 patients, two cases of herpes zoster occurred, and they received 400 mg acyclovir until the end of the fourth cycle. Their zoster occurred during the fifth cycle of bortezomib treatment (Table 2). No herpes zoster occurred from the patients who received 400 mg of acyclovir until the end of bortezomib treatment.

One hospital (SMC) used the reduced dose of acyclovir 200 mg once daily in 19 patients. They reduced the dosage when the patients' renal function was impaired or the patients were at risk of nephrotoxicity due to the concomitant use of potentially nephrotoxic drugs according to the dosage modification reported from the previous report (9). Among these 19 patients who received 200 mg once daily, five patients developed herpes zoster (Table 2). The onset of herpes zoster was within the third cycle of bortezomib treatment. Even though the baseline characteristics at the time of bortezomib treatment were balanced between two groups, the frequency of herpes zoster was significantly higher in 200 mg group than 400 mg ($P = 0.007$, Table 1). There were no adverse events associated with the use of acyclovir prophylaxis in these 80 patients.

The clinical pictures and outcomes were summarized in Table 2. Localized herpes zoster was dominant (6/7 cases), and only one patient showed disseminated zoster (Table 2). All patients were treated with therapeutic dosage of antiviral agents such as 750 mg of famciclovir once daily for 7–14 days. The response to anti-viral therapy was good, thus all patients got recovered, but four patients had a post-herpetic neuralgia. After anti-viral therapy, five patients could receive bortezomib treatment again, but two patients could not continue treatment due to the following reasons: disease progression and poor general condition after herpes zoster.

DISCUSSION

It remains still unclear how bortezomib can contribute to the reactivation of varicella zoster virus. However, it is clinically evident that the use of bortezomib increases the incidence of herpes zoster. The proposed mechanism of bortezomib-induced varicella zoster virus reactivation is associated with bortezomib-induced immune suppression. Thus, the proteasome inhibition was reported to suppress the activation of CD4-positive T cells resulting in impaired immune functions of T cells (11). Furthermore, a recent study showed that bortezomib could lead to a transient decrease in CD4-positive lymphocytes, accompanied by an increased incidence of varicella zoster virus infections (12). This increase of herpes zoster in myeloma patients receiving bortezomib led to the use of acyclovir as a prophylaxis in subsequent clinical trials (5,6). In a clinical trial from Spain, the overall incidence of herpes zoster was markedly decreased to 6.6% after the prophylaxis with acyclovir 400 mg three times daily was started (13). Thus, most recent trials have recommended the prophylactic dose of 400 mg three times daily. However, the minimal effective dose of prophylactic acyclovir for herpes zoster in patients receiving bortezomib has not yet been established.

Table 2. The summary of patients with herpes zoster

Sex	Age	Subtype	D-S stage	Serum Cr (g/dl)	ECOG PS	Previous therapy	Disease duration before bortezomib treatment (months)	Bortezomib regimen	Response to bortezomib	Acyclovir dose (mg)	Onset of herpes zoster	Pattern	Outcome	Restart bortezomib
Male	78	IgG, k	III	0.9	2	TCD	12.3	Vel/CD	PR	400	Fifth cycle	Localized	Recovered	Yes
Male	52	IgA, l	II	1.2	0	TCD	2.7	Vel/TCD	PR	400	Fifth cycle	Localized	Recovered	No
Male	69	IgG, k	III	0.8	1	CP	2.9	Vel/D	SD	200	First cycle	Disseminated	Recovered	Yes
Female	71	IgA, k	III	0.9	0	VAD→ASCT→TD	56.8	Vel/D	SD	200	First cycle	Localized	Recovered	Yes
Male	60	IgG, l	III	3.1	1	VAD→ASCT	15.5	Vel/D	PD	200	Second cycle	Localized	Recovered	No
Female	66	IgG, k	III	1.8	1	CP	3.0	Vel/D	CR	200	First cycle	Localized	Recovered	Yes
Female	64	IgG, l	III	3.5	2	VAD→CD	12.1	Vel/D	VGPR	200	Third cycle	Localized	Recovered	Yes

ASCT, autologous stem cell transplantation; Vel/D, bortezomib, dexamethasone; PAD, bortezomib, doxorubicin, dexamethasone; Vel/CD, bortezomib, cyclophosphamide, dexamethasone; Vel/TCD, bortezomib, thalidomide, cyclophosphamide, dexamethasone; VAD, vincristine, Adriamycin, dexamethasone; TCD, thalidomide, cyclophosphamide, dexamethasone; CD, cyclophosphamide, dexamethasone; CP, cyclophosphamide, prednisolone.

In our retrospective analysis, only seven cases of herpes zoster were observed from 80 patients (7/80, 8.75%). Although this incidence was much lower than that of our previous result reporting 22.3% of herpes zoster from patients who received bortezomib without acyclovir prophylaxis (4), our result was different from the previous reports showing no herpes zoster with the use of low-dose acyclovir (8,9). However, two cases of zoster occurred from patients who received 400 mg of acyclovir during the limited period from the first cycle to the fourth cycle. The other five cases occurred from patients received 200 mg of acyclovir (Table 2). Among these five patients, three patients had elevated serum creatinine level (3.5−1.8 g/dl) while the other two patients had normal serum creatinine (Table 2). Therefore, 200 mg of acyclovir may not be enough to prevent herpes zoster even if renal dysfunction may increase drug concentration in blood. However, no patients who received 400 mg of acyclovir till the last cycle of bortezomib treatment develop herpes zoster. Our results suggest that the dose of 400 mg once daily could prevent the occurrence of herpes zoster with the efficacy comparable to the conventional dose of acyclovir prophylaxis, 400 mg three times daily. However, the dosage reduction to 200 mg or shortening of prophylaxis duration might decrease the efficacy of acyclovir prophylaxis.

Our study population was relapsed myeloma patients or refractory to primary therapy. Furthermore, bortezomib was administered with other immune modulating drugs such as thalidomide, dexamethasone and cyclophosphamide. Although relapsed or refractory myeloma patients might have more deteriorated health status, and the combination of bortezomib with other drugs might increase the risk of adverse events, our results showed the low-dose acyclovir could be an effective prophylaxis irrespective of the disease status and the type of therapy administered.

In conclusion, we have shown that acyclovir 400 mg of acyclovir once daily was sufficient to prevent herpes zoster in Korean myeloma patients receiving bortezomib-containing chemotherapy as previous reports from Western people. Thus, we suggest the continuous administration of acyclovir 400 mg once daily during the bortezomib treatment as a prophylaxis for herpes zoster. To our knowledge, this is the first report about the efficacy of low-dose acyclovir prophylaxis in Asian people.

Conflict of interest statement

None declared.

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