Importance of Compliance With Guidelines for the Prevention of Varicella-Zoster Virus Reactivation in Multiple Myeloma

YASUKATA OHASHI^{1,2}, MEGUMI YATABE¹, DAISUKE NIIJIMA¹, ARINA IMAMURA¹,
YOSHIYUKI NAGAYAMA¹, KENTARO OTSUKA¹, YUTAKA YACHI¹, HIRONORI UENO³,
TAKAHIRO YANO³, NOBUAKI MORI⁴, KOJI HIGAI² and AKIHIRO YOKOYAMA^{3,5}

¹Department of Pharmacy, National Hospital Organization Tokyo Medical Center, Tokyo, Japan;

²Department of Medical Biochemistry, Faculty of Pharmaceutical Sciences, Toho University, Chiba, Japan;

³Division of Hematology, National Hospital Organization Tokyo Medical Center, Tokyo, Japan;

⁴Department of General Internal Medicine and Infectious Diseases,

National Hospital Organization Tokyo Medical Center, Tokyo, Japan;

⁵Division of Transfusion Medicine, National Hospital Organization Tokyo Medical Center, Tokyo, Japan

Abstract. *Background/Aim: The importance of compliance with National Comprehensive Cancer Network (NCCN) guidelines for preventing varicella-zoster virus reactivation (VZVr) in multiple myeloma (MM) in a clinical setting has not been well investigated. Patients and Methods: We retrospectively studied the clinical characteristics and outcomes of 118 patients with MM treated with proteasome inhibitors. Results: Thirty-nine episodes of VZVr were observed in 37 patients (VZVr group). The proportion of prophylactic antiviral prescriptions and compliance with antiviral prophylaxis based on the NCCN Clinical Practice guidelines was 76% and 30% in the VZVr group, and 88% and 74% in the non-VZVr group, respectively. Multivariate analysis showed that compliance with the NCCN guidelines was the only independent risk factor for VZVr ($p=0.0017$). Conclusion: It is important that prophylactic antivirals are prescribed for an appropriate duration of time to prevent the reactivation of VZV in compliance with existing guidelines.*

Multiple myeloma (MM) is an incurable refractory hematological disease, even in the era of novel anticancer agents. Bortezomib, the first proteasome inhibitor (PI), was approved in the United States (US) in May 2003 (in Japan

in December 2006), followed by carfilzomib in the US in July 2012 (in Japan in August 2016) and ixazomib in the US in November 2015 (in Japan in May 2017), which has become a key drug for MM treatment. In addition, with the recent introduction of monoclonal antibodies (mAbs) such as elotuzumab, daratumumab, and isatuximab, the number of treatment options has increased dramatically (1, 2).

Several reports have shown that bortezomib increases varicella-zoster virus (VZV) reactivation (3-6), and the National Comprehensive Cancer Network (NCCN) guidelines place PI at high risk of VZV reactivation. Prophylactic oral antivirals such as acyclovir (ACV), famciclovir, and valacyclovir (VACV) should be considered during treatment and the associated neutropenic period. The risk of reactivation in autologous stem cell transplantation (ASCT), which is important in the treatment of MM, is considered moderate, and prophylactic medication should be continued for at least 6 months to 1 year after transplantation (7). Although it has been reported that prophylactic antivirals should be administered for mAbs, such as elotuzumab and daratumumab (8), the NCCN guidelines do not recommend prophylaxis for mAbs used in the treatment of MM, and a consensus has not yet been reached. A number of reports have examined the efficacy of antivirals in preventing VZV reactivation in patients with MM who have received bortezomib and conventional chemotherapy (9-15). However, these reports lacked information on the extent to which the guidelines were followed, although they did mention whether or not prophylactic antivirals were prescribed.

The aim of the study was to determine the detailed incidence of VZV reactivation and its risk factors, taking into account the prescription status of prophylactic antivirals during the past 10 years, including the treatment era of new agents.

This article is freely accessible online.

Correspondence to: Yasukata Ohashi, Department of Pharmacy, National Hospital Organization Tokyo Medical Center, 2-5-1 Higashigaoka, Meguro-ku, Tokyo 152-8902, Japan. Tel: +81 334110111, Fax: +81 334115488, e-mail: yasu970554126@gmail.com

Key Words: Varicella-zoster virus reactivation, multiple myeloma, proteasome inhibitors, compliance, NCCN guidelines.

Patients and Methods

Patients and study design. This retrospective study evaluated MM patients who had started treatment, including PIs, and had been treated for at least 3 months at the National Hospital Organization Tokyo Medical Center (Tokyo, Japan) between July 2009 and June 2019. Patient information was obtained from medical records. We collected data on patient baseline characteristics, including age, sex, International Staging System (ISS) category at diagnosis, myeloma subtype, Charlson Comorbidity Index (CCI), number of lines of myeloma therapy, medical history of herpes zoster (HZ) infection, diabetes mellitus, and collagen disease; and hematologic parameters such as neutrophil count, lymphocyte count, hemoglobin, platelet counts, C-reactive protein (CRP), and creatinine. This study was performed according to the principles set out in the 1964 Declaration of Helsinki and all subsequent revisions and was approved by the Ethics Committee at National Hospital Organization Tokyo Medical Center (R20-107). The need for informed consent was waived by the ethics committee because the data were retrieved from electronic medical records.

Myeloma treatment and antiviral prophylaxis. We investigated the use of typical drugs used in treating myeloma and the number of ASCT performed. We also surveyed the use of prophylactic antivirals since the start of PI treatment and compliance to NCCN guidelines that met the definition described below.

Characteristics of VZV reactivation. We also investigated the frequency and timing of onset of VZV reactivation, treatment for VZV, and postherpetic neuralgia (PHN) in cases that met the definition described below. The severity of VZV infection was determined using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Incidence of and risk factors for VZV reactivation. The cumulative incidence rates of VZV reactivation and reactivation-free mortality were evaluated using Gray's method, considering both as a competing risk (16). Crude incidence rates of VZV reactivation per 100 person-years were calculated for each year since starting treatment with PIs. Person-time was censored at loss to follow-up, death, or 3 years after beginning treatment with PIs, whichever occurred first.

Definitions. VZV reactivation was defined as localized and disseminated HZ with a history of chickenpox. We could not obtain the anti-VZV immunoglobulin G serology of the patients. Localized HZ was defined in the presence of cutaneous vesicular lesions in a dermatomal distribution with or without confirmation of VZV by polymerase chain reaction. Disseminated HZ was defined as the subsequent appearance of lesions in non-contiguous dermatomes and/or visceral involvement. The occurrence of new episodes of VZV reactivation after complete resolution of a preceding episode or more than a week after adequate antiviral treatment was defined as recurrent VZV reactivation. The number of days until VZV reactivation was calculated using the date of PI initiation as the starting date. Antiviral prophylaxis was defined as patients in whom antiviral agents were prescribed for more than 4 weeks after the start of treatment with PIs. The proportion of prophylactic antiviral prescriptions covering the treatment period was calculated by dividing the total number of days from the start of prophylactic

antiviral prescription to the last prescription date by the number of days from the start of PIs to the last dose (or until recovery to less than grade 3 neutropenia when there was grade 3 or greater) or 6 months from the day of transplant in ASCT recipients. Compliance with the recommended period of prophylactic antivirals in the NCCN guideline was defined as in which prophylactic antiviral prescriptions were at least 80% of the PI treatment period, including the associated neutropenic periods, or at least 6 months post-transplantation in patients with ASCT. PHN was defined as dermatomal pain that persisted for more than 3 months after VZV reactivation (17). Recent treatment history was defined as the most recent treatment that had been performed for up to 6 months before VZV reactivation.

Statistical analysis. Fischer's exact test and Mann-Whitney *U*-test were used for between-group comparisons (univariate analysis) of categorical and numerical data, respectively. A multivariable model for the assessment of risk factors for VZV reactivation was constructed using logistic regression. All variables with *p*-values <0.15, in the univariate analyses, were included in the multivariate analysis. All *p*-values were two-sided, and *p*<0.05, was considered significant. All statistical analyses were performed using EZR version 1.40 (Saitama Medical Center, Jichi Medical University, Saitama, Japan) (18).

Results

Patient characteristics. One hundred twenty-two patients started with PI therapy between June 2009 and July 2019, of which four were excluded due to a treatment duration <3 months, for 118 patients. VZV reactivation was observed in 37 patients with 39 episodes (including two recurrences). At the cut-off of June 30, 2020, patients were followed-up for a median of 44.3 months [interquartile range (IQR)=21.2-67.6]. Patients were divided into two groups according to the presence (VZVr) or absence (non-VZVr) of VZV reactivation. As shown in Table I, there were no significant differences in the baseline characteristics between the two groups, except for age and hemoglobin levels.

Myeloma treatment and antiviral prophylaxis. Table II shows the treatment of myeloma and the prevention of VZV reactivation with antiviral drugs. Treatment with PIs was started with bortezomib in almost all patients, and only one patient in the non-VZVr group received induction therapy with carfilzomib and then no treatment after ASCT; therefore, there was no history of treatment with bortezomib. All other 15 patients were administered carfilzomib except 1, and all 18 patients were administered ixazomib in combination with lenalidomide and dexamethasone for relapsed and/or refractory conditions. Alkylating agents indicate the therapeutic regimen, including oral cyclophosphamide (VCD) or melphalan (MP). There were 19 ASCT recipients (51%) in the VZVr group and 22 (27%) in the non-VZVr group with a statistically significant difference (*p*=0.019). Regarding the duration of exposure by

Table I. Baseline patient characteristics.

Characteristic	VZVr group (n=37)	Non-VZVr group (n=81)	p-Value
Median age, Years (range)	65 (55-88)	68 (44-88)	0.015
Male sex, n (%)	19 (51)	43 (53)	1.00
ISS at initial diagnosis, n (%)			
I	12 (32)	16 (20)	0.41
II	15 (41)	35 (43)	
III	9 (24)	28 (35)	
Unknown	1 (3)	2 (2)	
Myeloma subtype, n (%)			
IgG	22 (59)	51 (63)	0.59
IgA	8 (22)	16 (20)	
BJP	5 (14)	10 (12)	
IgD	2 (5)	1 (1)	
Non-secretory	0 (0)	3 (4)	
Charlson Comorbidity Index, n (%)			
0	22 (59)	43 (53)	0.27
1	9 (24)	14 (17)	
≥2	6 (16)	24 (30)	
Number of lines of myeloma therapy, n (%)			
0	17 (46)	49 (60)	0.18
1	10 (27)	21 (26)	
2	4 (11)	7 (9)	
≥3	6 (16)	4 (5)	
Previous herpes zoster infection, n (%)	6 (16)	13 (16)	1.00
Prior history of diabetes mellitus, n (%)	4 (11)	14 (17)	0.42
Prior history of collagen disease, n (%)	2 (5)	1 (1)	0.23
Hematologic parameters, Median (IQR)			
ANC (×10 ⁹ /L)	2.60 (2.10-5.19)	2.87 (2.03-3.64)	0.90
ALC (×10 ⁹ /L)	1.20 (0.78-1.50)	1.13 (0.77-1.65)	0.69
CRP (mg/L)	0.10 (0.10-0.30)	0.20 (0.10-0.78)	0.23
Hemoglobin (g/dL)	10.3 (8.7-12.4)	9.2 (7.9-10.9)	0.02
Platelets (×10 ⁹ /L)	180 (160-221)	160 (137-217)	0.55
Creatinine (mg/dL)	0.80 (0.63-0.99)	0.91 (0.70-1.32)	0.22

Bold type denotes significance. The numbers in parentheses indicate percentages. VZVr, Varicella zoster virus reactivation; ISS, International Staging System; BJP, Bence Jones protein; IQR, interquartile range; ANC, absolute neutrophil count; ALC, absolute lymphocyte count; CRP, C-reactive protein.

each drug category, there was no significant difference, although immunomodulatory drugs (IMiDs) tended to be longer in the non-VZVr group. The majority of prophylactic antivirals prescribed were ACV 200 mg/day in 25 patients (68%) in the VZVr group and 65 patients (80%) in the non-VZVr group. No prophylactic antivirals were prescribed in nine patients (24%) in the VZVr group and 10 patients (12%) in the non-VZVr group. The median proportion of prophylactic antiviral prescriptions covering the treatment

Table II. Myeloma treatment and antiviral prophylaxis.

Characteristic	VZVr group (n=37)	Non-VZVr group (n=81)	p-Value
Myeloma treatment, n (%)			-
PIs			
Bortezomib	37 (100)	80 (99)	
Carfilzomib	5 (14)	11 (14)	
Ixazomib	6 (16)	12 (15)	
IMiDs			
Thalidomide	10 (27)	17 (21)	
Lenalidomide	29 (78)	62 (77)	
Pomalidomide	5 (14)	18 (22)	
mAbs			
Elotuzumab	0 (0)	3 (4)	
Daratumumab	5 (14)	8 (10)	
Panobinostat	0 (0)	1 (1)	
Alkylating agents (oral)	20 (54)	20 (25)	
Dexamethasone	37 (100)	80 (99)	
Autologous stem cell transplantation	19 (51)	22 (27)	0.019
Median exposure duration, Days (IQR)			
PIs	385 (269-1,015)	358 (116-780)	0.23
IMiDs	146 (30-603)	442 (39-934)	0.17
mAbs	160 (104-196)	168 (84-322)	0.74
Antiviral prophylaxis, n (%)			0.14
Acyclovir 200mg/day	25 (68)	65 (80)	
Acyclovir 400mg/day	2 (5)	1 (1)	
Valacyclovir 500mg/day	1 (3)	5 (6)	
None	9 (24)	10 (12)	
Compliance with NCCN guideline, n (%)			<0.001
Yes	11 (30)	60 (74)	
No	26 (70)	21 (26)	

Bold type denotes significance. The numbers in parentheses indicate percentages. VZVr, Varicella zoster virus reactivation; PI, proteasome inhibitor; IMiDs, immunomodulatory drugs; mAbs, monoclonal antibodies; IQR, interquartile range; NCCN, National Comprehensive Cancer Network.

period was 42% (IQR=0-100) in the VZVr group and 100% (IQR=68.9-100) in the non-VZVr group. Compliance with the provisions of the NCCN guidelines for prophylactic antivirals was statistically significant in 11 patients (30%) in the VZVr group and 60 patients (74%) in the non-VZVr group ($p<0.001$).

Characteristics of VZV reactivation. The median time from initiation of treatment with PIs to VZV reactivation was 353 days (IQR=106-634). Of the five patients who had been prescribed prophylactic antivirals at the time of VZV reactivation, one was more than 1 year after ASCT, and four were on bortezomib therapy, as shown in Table III. In addition, VZV reactivation was localized in 33 episodes

Table III. Characteristics of varicella zoster virus infection episodes in patients with myeloma.

Characteristic	n=39*
Administration of antiviral medication at the reactivation, n (%)	
Yes	5 (13)
No	34 (87)
Type of infection, n (%)	
Localized	33 (85)
Disseminated	6 (15)
Grade of infection(CTCAE ver 5.0), n (%)	
1	3 (8)
2	26 (67)
3	10 (26)
ALC ($\times 10^9/l$), Median (IQR)	1.20 (0.87-1.64)
Myeloma treatment period, n (%)	
Induction	11 (30)
ASCT	14 (36)
Plateau	3 (8)
Relapse	6 (15)
Treatment-free duration after remission	5 (14)
Recent treatment, n (%)	
None	18 (46)
PI+DEX	13 (33)
PI+Alkylating agent+DEX	3 (8)
PI+IMiDs+DEX	2 (5)
IMiDs+DEX	3 (8)
VZV treatment, n (%)	
Acyclovir IV	10 (26)
Acyclovir PO	4 (11)
Valacyclovir	17 (44)
Famcyclovir	4 (11)
Amenamavir	2 (5)
Topical medicine only	2 (5)
Postherpetic Neuralgia, n (%)	
Yes	13 (33)
No	25 (64)
Unknown	1 (3)

*Because multiple VZV reactivation was recorded in the same patient, this Table includes 39 episodes in 37 patients. The numbers in parentheses indicate percentages. VZV, Varicella zoster virus; CTCAE, Common Terminology Criteria for Adverse Events; ALC, absolute lymphocyte count; IQR, interquartile range; ASCT, autologous stem cell transplantation; PI, proteasome inhibitor; DEX, dexamethasone; IMiDs, immunomodulatory drugs; IV, intravenous injection; PO, per os.

(85%) and disseminated in six episodes (15%). According to the CTCAE version 5.0, there were no fatal infections, but there were eight grade 3 infections (20%) that required hospitalization. As for the treatment status at the time of VZV reactivation, ASCT was the most common treatment with 14 episodes (36%), followed by 11 episodes (30%) of induction therapy. The ASCT included 12 patients who were in treatment-free follow-up after ASCT and two patients on maintenance therapy. Nine of the 12 patients had their prophylactic antiviral prescriptions discontinued less than six months after ASCT. The most recent treatment at the time of

Figure 1. Cumulative incidence of VZV reactivation after treatment with PIs. Censored patients are marked on the curves with a cross. VZV, Varicella zoster virus; PI, proteasome inhibitor.

VZV reactivation was no treatment for 18 episodes (46%), and these mostly occurred during the treatment-free observation period after ASCT and induction therapy. PHN as a complication after HZ was observed in 12 patients (13 episodes), 11 of whom underwent ASCT. Six of these patients continued to have neuropathic pain and were prescribed with analgesics, such as pregabalin. No grade 4 or 5 patients due to VZV reactivation were observed. All six patients diagnosed with disseminated HZ were hospitalized and required intravenous ACV treatment, and one of them had swelling and severe pain in the left auricle, which was initially suspected to be Ramsay Hunt syndrome. Since there was no obvious facial paralysis afterwards, a definitive diagnosis was not made, but it took 127 days before the planned treatment could be resumed.

Incidence of and risk factors for VZV reactivation. The cumulative incidence of VZV reactivation after starting treatment with PIs was 16.5% [95% confidence interval (CI)=10.2-23.5] after 1 year and 36.5% (95% CI=26.4-46.6) during the observation period (Figure 1). The two cases with recurrent VZV reactivation were counted as events in the first reactivation. In addition, the incidence rate during the 3-year observation period was calculated using the person-year method to ascertain VZV reactivation status in each year of treatment with PIs. The 3-year incidence rate in 2009 was the highest at 27.5/100 person-years, and since 2010, the rates have been 14.0, 8.8, 14.3, 17.2, 10.5, 16.0, and 18.1 (Figure 2). Multivariate analysis showed that compliance with the NCCN guidelines was the only independent risk

Figure 2. The 3-year-incidence rates (per 100 person-years) of VZV reactivation after starting treatment with PIs. Crude incidence rates of VZV reactivation per 100 person-years were calculated for each year of starting treatment with PIs. Person-time was censored at loss to follow-up, death, or 3 years after starting treatment with PIs, whichever occurred first. VZV, Varicella zoster virus; PI, proteasome inhibitor.

factor for VZV reactivation (odds ratio=0.17; 95% CI=0.054-0.51, $p=0.0017$) (Table IV).

Discussion

To the best of our knowledge, this is the first report discussing the usefulness of compliance with the NCCN GL in preventing VZV reactivation using real-world data in Japan. In addition, this study was more detailed than previous reports, as it investigated not only the frequency of VZV reactivation after PI treatment, but also anticancer drug treatment for MM at the onset, treatment for HZ, and the frequency of PHN as a sequela, through long-term observation.

The proportion of VZV reactivation during the overall period of our study was 31.4% (37/118), which was higher than that previously reported in patients treated with bortezomib (0-16.7%), but the proportion of reactivation at one year of PI treatment was 16.1% (19/118), which was similar to that reported previously (3, 9-12). This may be due to differences in the median observation period (44.3 months in our study vs. 3.8-8.3 months in previous reports), that in the proportion of prophylactic antivirals prescribed [84% (99/118) vs. 0-100%], and the impact of ASCT and subsequent treatment in case of relapse (3, 9-12). In addition, the recommended daily dose of ACV for prophylactic use in the US and Europe is 800 mg (19); however, in our study, a lower dose of 200 mg was prescribed in 91% (90/99) of patients. In previous studies in patients treated with ASCT (14), allogeneic SCT (20), and bortezomib (21), including MM patients, 200 mg/day of ACV has been reported to be

Table IV. Multivariate analysis of the risk factors for varicella zoster virus reactivation.

Variables	Odds ratio	95% CI	p-Value
Age (≥ 65 years)	0.60	0.20-1.85	0.38
Hemoglobin (≥ 10 g/dl)	0.86	0.33-2.24	0.75
ASCT	1.79	0.55-5.83	0.33
Antiviral prophylaxis	0.96	0.27-3.49	0.95
Compliance with NCCN guideline	0.17	0.054-0.51	0.0017

Bold type denotes significance. CI, Confidence interval ASCT, Autologous stem cell transplantation; NCCN, National Comprehensive Cancer Network.

effective in preventing VZV reactivation. On the other hand, there are only few reports suggesting that 200 mg/day ACV is insufficient to prevent VZV reactivation and that a dose of 400 mg/day or higher is recommended (12). There are also reports on the prevention of VZV reactivation by VACV as an antiviral drug other than ACV (22-24), since there was no difference between the VZVr and Non-VZVr groups with regard to the type of prophylactic antivirals, as shown in Table II, we speculate that neither the type nor dose of prophylactic antivirals had a significant effect on VZV reactivation. The frequency and duration of IMiDs prescriptions are increasing, regardless of the indication for ASCT (25). Although IMiDs themselves have been reported to increase the risk of VZV reactivation (26), there were only five episodes (13%) of VZV reactivation during treatment with IMiDs, including the combination with PIs in our study.

As shown in Figure 2, a comparison of the 3-year reactivation rates for each year of PI initiation shows that 2009 was higher than in later years. The first case series of VZV reactivation by bortezomib was reported in 2005 (27), and a detailed analysis of VZV reactivation was reported in 2008 as an ancillary study to a large-scale clinical trial (APEX) (3). However, at that time, there was still a lack of evidence for the prevention of VZV reactivation, and the 2007 version of the NCCN guidelines did not include prophylactic antivirals during treatment with bortezomib, which was recommended in the 2012 version (28). As a result, we estimate that even in 2009, the frequency of prophylactic antiviral prescriptions was low and the rate of VZV reactivation was high. Out of the 11 myeloma patients who were on induction therapy at the time of VZV reactivation, five had started treatment with bortezomib in 2009, and all had VZV reactivation early in treatment without prophylactic antiviral prescriptions (Table III). One of the reasons for the subsequent decline in the rate of reactivation may be that prophylactic administration of ACV with bortezomib was approved for insurance coverage in September 2011 in Japan. Furthermore, since around 2010, pharmacists in our hospital have been actively checking

individual prescriptions for both inpatients and outpatients, which may have contributed to a reduction in the number of missed prescriptions for prophylactic antivirals. More than half of the VZV reactivation occurred within 1 year of PI initiation (Figure 1), mainly during the treatment-free follow-up period after ASCT or initial treatment remission. The five guideline-compliant cases of VZV reactivation while continuing prophylactic antiviral prescriptions included two early after the start of induction therapy, one during the plateau phase after initiation of induction therapy, one during the first relapse therapy after induction therapy, and one during the first relapse therapy after tandem ASCT. Three of the patients, except for the two who reactivated early in the course of treatment with induction, reactivated after more than a year of treatment, and may have had poor adherence to prophylactic antivirals, although they had been prescribed.

PHN was the most common complication of VZV reactivation and was observed in 12 patients (13 episodes, 33%) in our study. Some of the patients had severe and persistent neuropathic pain and were prescribed analgesics such as pregabalin for more than half a year to reduce their quality of life. Although there were no fatal cases of VZV reactivation in our study, its prevention is important because there have been a small number of deaths in the general population (29), and some deaths have been reported in the absence of prophylactic medication, particularly in transplant recipients (30).

Recombinant zoster vaccine (RZV), which has already been approved in Europe and the US, was reported to have an efficacy rate of 68.2% in a prospective randomized clinical trial examining the efficacy of RZV in ASCT cases including MM (31). RZV became available in Japan in January 2020; therefore, it was not yet available during the study period, and there were no cases of routine RZV administration. In addition, some reports have already proposed measures incorporating RZV to prevent VZV reactivation after ASCT (7, 32). There were three cases of VZV reactivation after discontinuation of prophylactic antivirals more than one year after ASCT in our study, and similar cases have been reported in previous reports (30). Therefore, it is difficult to completely control reactivation by prophylactic antivirals alone, and prevention strategies combined with vaccination should be considered in the future in Japan.

Our study had several limitations. First, because it was a single-center, retrospective observational study, there was a selection bias. Second, prophylactic antivirals are only a prescribing history, and although pharmacists were interviewed in many cases during inpatient and outpatient treatment, they did not always confirm patient adherence in all cases. Finally, because our center did not have mandatory serological testing for VZV before ASCT, we could not strictly distinguish between primary and reactivated episodes of HZ.

In conclusion, we conducted a detailed analysis of VZV reactivation in MM patients with a history of PI treatment in the past 10 years, while taking into account the prescription status of prophylactic antivirals. In addition to prescribing prophylactic antivirals, it may be important that they be used for an appropriate period in accordance with the guidelines.

Conflicts of Interest

The Authors declare that they have no competing interests.

Authors' Contributions

YO and AY designed the study. YO, NM, YY, and AY prepared the manuscript. YO, MY, DN, AI, YN, KO, HU, TY, and AY collected the clinical data. YO and KH analyzed the data. All Authors have read and approved the final version of the manuscript.

References

- Anderson KC: Progress and paradigms in multiple myeloma. *Clin Cancer Res* 22(22): 5419-5427, 2016. PMID: 28151709. DOI: 10.1158/1078-0432.CCR-16-0625
- Durer C, Durer S, Lee S, Chakraborty R, Malik MN, Rafae A, Zar MA, Kamal A, Rosko N, Samaras C, Valent J, Chaulagain C and Anwer F: Treatment of relapsed multiple myeloma: Evidence-based recommendations. *Blood Rev* 39: 100616, 2020. PMID: 31500848. DOI: 10.1016/j.blre.2019.100616
- Chanan-Khan A, Sonneveld P, Schuster MW, Stadtmauer EA, Facon T, Harousseau JL, Ben-Yehuda D, Lonial S, Goldschmidt H, Reece D, Neuwirth R, Anderson KC and Richardson PG: Analysis of herpes zoster events among bortezomib-treated patients in the phase III APEX study. *J Clin Oncol* 26(29): 4784-4790, 2008. PMID: 18711175. DOI: 10.1200/JCO.2007.14.9641
- Kim SJ, Kim K, Kim BS, Lee HJ, Kim H, Lee NR, Nam SH, Kwon JH, Kim HJ, Sohn SK, Won JH, Lee JH, Suh C, Yoon SS, Kim HJ, Kim I, Do YR, Lee WS, Joo YD, Shin HJ and Korean Multiple Myeloma Working Party: Bortezomib and the increased incidence of herpes zoster in patients with multiple myeloma. *Clin Lymphoma Myeloma* 8(4): 237-240, 2008. PMID: 18765311. DOI: 10.3816/CLM.2008.n.031
- Reece DE, Rodriguez GP, Chen C, Trudel S, Kukreti V, Mikhael J, Pantoja M, Xu W and Stewart AK: Phase I-II trial of bortezomib plus oral cyclophosphamide and prednisone in relapsed and refractory multiple myeloma. *J Clin Oncol* 26(29): 4777-4783, 2008. PMID: 18645194. DOI: 10.1200/JCO.2007.14.2372
- Tong Y, Qian J, Li Y, Meng H and Jin J: The high incidence of varicella herpes zoster with the use of bortezomib in 10 patients. *Am J Hematol* 82(5): 403-404, 2007. PMID: 17133426. DOI: 10.1002/ajh.20838
- Prevention and treatment of cancer-related infections ver.2.2020. Available at: https://www.nccn.org/professionals/physician_gls/pdf/infections.pdf [Last accessed on June 6, 2021]
- Drgona L, Gudiol C, Lanini S, Salzberger B, Ippolito G and Mikulska M: ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the safety of targeted and biological therapies: an infectious diseases

- perspective (Agents targeting lymphoid or myeloid cells surface antigens [II]: CD22, CD30, CD33, CD38, CD40, SLAMF-7 and CCR4). *Clin Microbiol Infect* 24 Suppl 2: S83-S94, 2018. PMID: 29572070. DOI: 10.1016/j.cmi.2018.03.022
- 9 Pour L, Adam Z, Buresova L, Krejci M, Krivanova A, Sandecka V, Zahradova L, Buchler T, Vorlicek J and Hajek R: Varicella-zoster virus prophylaxis with low-dose acyclovir in patients with multiple myeloma treated with bortezomib. *Clin Lymphoma Myeloma* 9(2): 151-153, 2009. PMID: 19406726. DOI: 10.3816/CLM.2009.n.036
- 10 Swaika A, Paulus A, Miller KC, Sher T, Almyroudis NG, Ball D, Wood M, Masood A, Lee K and Chanan-Khan AA: Acyclovir prophylaxis against varicella zoster virus reactivation in multiple myeloma patients treated with bortezomib-based therapies: a retrospective analysis of 100 patients. *J Support Oncol* 10(4): 155-159, 2012. PMID: 22222250. DOI: 10.1016/j.suponc.2011.10.006
- 11 Vickrey E, Allen S, Mehta J and Singhal S: Acyclovir to prevent reactivation of varicella zoster virus (herpes zoster) in multiple myeloma patients receiving bortezomib therapy. *Cancer* 115(1): 229-232, 2009. PMID: 19090004. DOI: 10.1002/cncr.24006
- 12 Kim SJ, Kim K, Do YR, Bae SH, Yang DH and Lee JJ: 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. *Jpn J Clin Oncol* 41(3): 353-357, 2011. PMID: 20947927. DOI: 10.1093/jjco/hyq194
- 13 Truong Q, Veltri L, Kanate AS, Hu Y, Craig M, Hamadani M and Cumpston A: Impact of the duration of antiviral prophylaxis on rates of varicella-zoster virus reactivation disease in autologous hematopoietic cell transplantation recipients. *Ann Hematol* 93(4): 677-682, 2014. PMID: 24097085. DOI: 10.1007/s00277-013-1913-z
- 14 Kawamura K, Hayakawa J, Akahoshi Y, Harada N, Nakano H, Kameda K, Ugai T, Wada H, Yamasaki R, Ishihara Y, Sakamoto K, Ashizawa M, Sato M, Terasako-Saito K, Kimura S, Kikuchi M, Nakasone H, Yamazaki R, Kanda J, Kako S, Tanihara A, Nishida J and Kanda Y: Low-dose acyclovir prophylaxis for the prevention of herpes simplex virus and varicella zoster virus diseases after autologous hematopoietic stem cell transplantation. *Int J Hematol* 102(2): 230-237, 2015. PMID: 25990803. DOI: 10.1007/s12185-015-1810-4
- 15 Teh BW, Harrison SJ, Worth LJ and Slavin MA: Antiviral prophylaxis for varicella zoster virus infections in patients with myeloma in the era of novel therapies. *Leuk Lymphoma* 57(7): 1719-1722, 2016. PMID: 26727243. DOI: 10.3109/10428194.2015.1106538
- 16 Gooley TA, Leisenring W, Crowley J and Storer BE: Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. *Stat Med* 18(6): 695-706, 1999. PMID: 10204198. DOI: 10.1002/(sici)1097-0258(19990330)18:6<695::aid-sim60>3.0.co;2-o
- 17 Sampathkumar P, Drage LA and Martin DP: Herpes zoster (shingles) and postherpetic neuralgia. *Mayo Clin Proc* 84(3): 274-280, 2009. PMID: 19252116. DOI: 10.1016/S0025-6196(11)61146-4
- 18 Kanda Y: Investigation of the freely available easy-to-use software 'EZ' for medical statistics. *Bone Marrow Transplant* 48(3): 452-458, 2013. PMID: 23208313. DOI: 10.1038/bmt.2012.244
- 19 Teh BW, Slavin MA, Harrison SJ and Worth LJ: Prevention of viral infections in patients with multiple myeloma: the role of antiviral prophylaxis and immunization. *Expert Rev Anti Infect Ther* 13(11): 1325-1336, 2015. PMID: 26489539. DOI: 10.1586/14787210.2015.1083858
- 20 Asano-Mori Y, Kanda Y, Oshima K, Kako S, Shinohara A, Nakasone H, Sato H, Watanabe T, Hosoya N, Izutsu K, Asai T, Hangaishi A, Motokura T, Chiba S and Kurokawa M: Long-term ultra-low-dose acyclovir against varicella-zoster virus reactivation after allogeneic hematopoietic stem cell transplantation. *Am J Hematol* 83(6): 472-476, 2008. PMID: 18266207. DOI: 10.1002/ajh.21152
- 21 Minarik J, Pika T, Bacovsky J, Langova K and Scudla V: Low-dose acyclovir prophylaxis for bortezomib-induced herpes zoster in multiple myeloma patients. *Br J Haematol* 159(1): 111-113, 2012. PMID: 22816982. DOI: 10.1111/j.1365-2141.2012.09233.x
- 22 Klein A, Miller KB, Sprague K, DesJardin JA and Snyderman DR: A randomized, double-blind, placebo-controlled trial of valacyclovir prophylaxis to prevent zoster recurrence from months 4 to 24 after BMT. *Bone Marrow Transplant* 46(2): 294-299, 2011. PMID: 20421867. DOI: 10.1038/bmt.2010.99
- 23 Oshima K, Takahashi T, Mori T, Matsuyama T, Usuki K, Asano-Mori Y, Nakahara F, Okamoto S, Kurokawa M and Kanda Y: One-year low-dose valacyclovir as prophylaxis for varicella zoster virus disease after allogeneic hematopoietic stem cell transplantation. A prospective study of the Japan Hematology and Oncology Clinical Study Group. *Transpl Infect Dis* 12(5): 421-427, 2010. PMID: 20626711. DOI: 10.1111/j.1399-3062.2010.00541.x
- 24 Fukushima T, Sato T, Nakamura T, Iwao H, Nakajima A, Miki M, Sakai T, Kawanami T, Sawaki Y, Fujita Y, Tanaka M, Masaki Y, Okazaki T, Nakajima H, Motoo Y and Umehara H: Daily 500 mg valacyclovir is effective for prevention of Varicella zoster virus reactivation in patients with multiple myeloma treated with bortezomib. *Anticancer Res* 32(12): 5437-5440, 2012. PMID: 23225448.
- 25 Rajkumar SV and Kumar S: Multiple myeloma current treatment algorithms. *Blood Cancer J* 10(9): 94, 2020. PMID: 32989217. DOI: 10.1038/s41408-020-00359-2
- 26 König C, Kleber M, Reinhardt H, Knop S, Wäsch R and Engelhardt M: Incidence, risk factors, and implemented prophylaxis of varicella zoster virus infection, including complicated varicella zoster virus and herpes simplex virus infections, in lenalidomide-treated multiple myeloma patients. *Ann Hematol* 93(3): 479-484, 2014. PMID: 24318541. DOI: 10.1007/s00277-013-1951-6
- 27 Wu KL, van Wieringen W, Vellenga E, Zweegman S, Lokhorst HM and Sonneveld P: Analysis of the efficacy and toxicity of bortezomib for treatment of relapsed or refractory multiple myeloma in community practice. *Haematologica* 90(7): 996-997, 2005. PMID: 15996946.
- 28 Baden LR, Bensinger W, Angarone M, Casper C, Dubberke ER, Freifeld AG, Garzon R, Greene JN, Greer JP, Ito JI, Karp JE, Kaul DR, King E, Mackler E, Marr KA, Montoya JG, Morris-Engemann A, Pappas PG, Rolston K, Segal B, Seo SK, Swaminathan S, Naganuma M, Shead DA and National Comprehensive Cancer Network: Prevention and treatment of cancer-related infections. *J Natl Compr Canc Netw* 10(11): 1412-1445, 2012. PMID: 23138169. DOI: 10.6004/jncn.2012.0146

- 29 Bricout H, Haugh M, Olatunde O and Prieto RG: Herpes zoster-associated mortality in Europe: a systematic review. *BMC Public Health* 15: 466, 2015. PMID: 25940080. DOI: 10.1186/s12889-015-1753-y
- 30 Erard V, Guthrie KA, Varley C, Heugel J, Wald A, Flowers ME, Corey L and Boeckh M: One-year acyclovir prophylaxis for preventing varicella-zoster virus disease after hematopoietic cell transplantation: no evidence of rebound varicella-zoster virus disease after drug discontinuation. *Blood* 110(8): 3071-3077, 2007. PMID: 17515400. DOI: 10.1182/blood-2007-03-077644
- 31 Bastidas A, de la Serna J, El Idrissi M, Oostvogels L, Quittet P, López-Jiménez J, Vural F, Pohlreich D, Zuckerman T, Issa NC, Gaidano G, Lee JJ, Abhyankar S, Solano C, Perez de Oteyza J, Satlin MJ, Schwartz S, Campins M, Rocci A, Vallejo Llamas C, Lee DG, Tan SM, Johnston AM, Grigg A, Boeckh MJ, Campora L, Lopez-Fauqued M, Heineman TC, Stadtmauer EA, Sullivan KM and ZOE-HSCT Study Group Collaborators: Effect of recombinant zoster vaccine on incidence of herpes zoster after autologous stem cell transplantation: a randomized clinical trial. *JAMA* 322(2): 123-133, 2019. PMID: 31287523. DOI: 10.1001/jama.2019.9053
- 32 Lee CJ, Savani BN and Ljungman P: Varicella zoster virus reactivation in adult survivors of hematopoietic cell transplantation: How do we best protect our patients? *Biol Blood Marrow Transplant* 24(9): 1783-1787, 2018. PMID: 29653205. DOI: 10.1016/j.bbmt.2018.04.003

Received June 6, 2021

Revised July 15, 2021

Accepted August 20, 2021