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Prophylactic Efficacy Against Herpes Zoster and Costs Difference Between Acyclovir and Valaciclovir in Hematological Patients

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Abstract. *Background: Immunocompromised hematological patients are at increased risk of herpes zoster (HZ). We examined the efficacy of acyclovir and valaciclovir in preventing HZ. We also created a simulation to reduce prophylactic medicine costs. Patients and Methods: We retrospectively evaluated 573 hematological patients who received chemotherapy, and assessed the difference in the costs between the acyclovir (Zovirax®) and valaciclovir (Valtrex®) groups. Results: Forty-four out of the 573 patients (7.7%) developed HZ. Out of them, there were 37 patients (84.1%) who received corticosteroids. Moreover, in total, there were 67 patients receiving acyclovir prophylaxis and 42 patients receiving valaciclovir prophylaxis, out of which one from each group occurred with HZ. The total 5-year cost of acyclovir and valaciclovir was ¥2,869,917 and ¥4,809,952, respectively. Therefore, by changing from valaciclovir to acyclovir, medical costs could be reduced by 28.3%. Additionally, switching to generic inexpensive acyclovir would possibly reduce them to 15.0%. Conclusion: Chemotherapy, including corticosteroids, is associated with a high incidence of HZ. Additionally, there was no prophylactic difference between acyclovir and valaciclovir. We expect that use of generic acyclovir could reduce prophylaxis costs by 85.0%.*

Chemotherapy treatments for hematological patients are intensive, and the relative dose intensity (RDI) is not reduced. Therefore, they often experience complications, such as bacterial, fungal, or viral infections, due to their immunodeficient state. This may reduce patient quality of life and the treatment's effect. Specifically, herpes zoster (HZ) re-activation can result in post-herpetic neuralgia, reduction of quality of life, or even chemotherapy discontinuation. There are reports on the risk factors and the prevention of HZ in patients with multiple myeloma (MM) treated with bortezomib, that show that acyclovir and valaciclovir reduce the risk of HZ (1, 2). Additionally, there are reports of patients with malignant lymphoma treated with rituximab, purine analog, and autologous stem-cell transplantation (3-7). However, the optimal dose of antiviral agent varies and there are a few reports on valaciclovir prophylaxis. Consequently, the aim of this retrospective analysis was to evaluate HZ frequency and the efficacy of acyclovir and valaciclovir prophylaxis in a population of hematological patients treated with chemotherapy at our hospital. We also created simulation that reduces the prophylactic medicine costs.

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Key Words: Herpes zoster, acyclovir, valaciclovir, prophylactic medicine costs.

Patients and Methods

Patients. The subjects of this study were 573 hematological patients who received chemotherapy at the Ogaki Municipal Hospital (Ogaki-shi, Japan) between January 2011 and December 2015. This study was reviewed and approved by the Ethics Committee at Ogaki Municipal Hospital (20150827-3).

Background of patients. The backgrounds of the patients who developed HZ were investigated for gender, age, diagnosis, treatment, number of treatment times, and prophylactic administration of antiviral medicines. The backgrounds between the acyclovir (Zovirax®) and the valaciclovir (Valtrex®) groups are compared.

Difference in prophylaxis costs. We assessed the difference of the prophylaxis period and costs of medicine between the acyclovir- and valaciclovir-treated groups. We also created a simulation for prophylactic medicine costs that offers considerable savings. The costs were calculated by using Japanese medicine prices of December 2015.

Table I. *Characteristics of patients with herpes zoster.*

Characteristic	With herpes zoster		Without herpes zoster		*p*-Value
	No.	%	No.	%	
Number of patients	44		529		
Gender					0.432
Male	22	50.0	285	53.9	
Female	22	50.0	244	46.1	
Age, years					0.977
Median (range)	72 (19-89)		69 (16-94)		
>65	31	70.5	319	60.3	
Diagnosis					
Malignant lymphoma					
Non-Hodgkin's lymphoma	28	63.6	282	53.3	0.194
Hodgkin's lymphoma	0	0.0	16	3.0	0.242
Multiple myeloma	9	20.5	91	17.2	0.868
Leukemia					
Acute myeloid leukemia	4	9.1	47	8.9	0.963
Acute promyeloid leukemia	0	0.0	11	2.1	0.334
Acute lymphoblastic leukemia	2	4.5	11	2.1	0.291
Chronic myelogenous leukemia	0	0.0	32	6.0	0.093
Chronic lymphocytic leukemia	0	0.0	6	1.1	0.477
Hairy cell leukemia	1	2.3	2	0.4	0.094
Melodysplastic syndromes	0	0.0	17	3.2	0.227
Other	0	0.0	14	2.6	-
Treatment					
With corticosteroids	37	84.1	359	67.9	0.327
With rituximab	16	36.4	230	43.5	0.741
With bortezomib	5	11.4	50	9.5	0.276
With bendamustine	2	4.5	16	3.0	0.578
Prior autologous stem cell transplantation	3	6.8	7	1.3	0.007
Number of chemotherapy courses at onset herpes zoster					
1	24	54.5			
2	10	22.7			
3	2	4.5			
4	3	6.8			
5	2	4.5			
>5	3	6.8			
Prophylaxis					0.736
Acyclovir (Zovirax®)	1	2.3	66	12.5	
Valaciclovir (Valtrex®)	1	2.3	41	7.8	
Nothing	42	95.5	422	79.8	

Statistical analysis. The data were analyzed using JMP software (version 5.0.1J; SAS Institute Japan Ltd., Tokyo, Japan). The Mann-Whitney *U*-test was used for comparison of the backgrounds of the patients between the groups. The recorded *p*-values were two-sided, and $p<0.05$ was considered to indicate a statistically significant difference.

Results

Patient background. Forty-four out of the 573 patients (7.7%) developed HZ. The baseline characteristics of the 573 patients are listed in Table I. One patient from each of the acyclovir and valaciclovir prophylaxis groups developed HZ; the other 42 patients did not receive prophylaxis (42/44, 95.5%). Twenty-eight patients (28/44, 63.6%) had non-Hodgkin's lymphoma (NHL), and nine (9/44, 20.5%) had multiple myeloma (MM). A total of 84.1% of patients received chemotherapy, including corticosteroids, 36.4% received rituximab and 11.4% bortezomib. Twenty-four (24/44, 54.5%) patients were observed within one cycle of chemotherapy.

Antivirus prophylaxis. Table II summarizes the characteristics of patients who received antivirus prophylaxis. There were 67 patients receiving acyclovir and 42 patients receiving

Table II. *Characteristics of patients who received antivirus prophylaxis.*

Characteristic	With acyclovir		With valaciclovir		*p*-Value
	No.	%	No.	%	
Number of patients	67		42		
Herpes zoster					0.736
Occurrence	1	1.5	1	2.4	
None	66	98.5	41	97.6	
Gender					0.682
Male	34	50.7	23	54.8	
Female	33	49.3	19	45.2	
Age, years					0.706
Median (range)	73 (19-90)		74 (44-87)		
>65	54	80.6	34	81.0	
Diagnosis					
Malignant lymphoma	15	22.4	24	57.1	<0.001
Multiple myeloma	49	73.1	15	35.7	<0.001
Other	3	4.5	3	7.1	
Treatment					
With corticosteroids	53	79.1	30	71.4	0.361
With rituximab	15	22.4	18	42.9	0.023
With bortezomib	48	71.6	10	23.8	<0.001
With bendamustine	11	16.4	8	19.0	0.724
Prior autologous stem cell transplantation	6	9.0	3		0.737
Previous zoster history					<0.001
Absence	62	92.5	27	61.4	
Presence	5	7.5	15	34.1	
Duration of prophylaxis, days					0.023
Total	12,003		11,025		
Median (range)	202 (9-1103)		143 (20-563)		
Costs of prophylactic medicines, ¥					<0.001
Total	2,869,917		4,809,952		
Median (range)	34,191 (4,782-134,613)		88,290 (3,924-480,908)		

¥, Japanese yen.

valaciclovir prophylaxis. Out of these, 49 (49/67, 73.1%) had MM and 15 (15/67, 22.4%) had NHL in the acyclovir group, compared to 15 (15/42, 35.7%) and 24 (24/42, 57.1%) patients in the valaciclovir group, respectively. Patients received acyclovir prophylaxis orally at a dose of 200 mg or 500 mg of valaciclovir daily. In the acyclovir group, the number of patients with MM was significantly higher than that of other patients ($p<0.001$). On the other hand, in the valaciclovir group, patients with NHL were significantly more frequent ($p<0.001$). Considering treatment, the proportion of acyclovir-treated patients administered bortezomib was significantly higher ($p<0.001$). Moreover, there were significantly more patients who had a history of HZ in the valaciclovir group ($p<0.001$).

Difference in prophylaxis period and medicine costs. The median duration of acyclovir, and valaciclovir prophylaxis was 202 days (range=9-1103 days) and 143 days (range=20-563 days), respectively. The median cost of prophylaxis using acyclovir and valaciclovir per person was ¥34,191 (range=¥4,782-134,613) and ¥88,290 (range=¥3,924-480,908), respectively, while the total cost was ¥2,869,917 and ¥4,809,952, respectively.

Simulation for reducing cost of prophylaxis medicines. Table III summarizes the simulation for saving prophylactic medicine costs. Changing valaciclovir to acyclovir would possibly reduce medical costs by 28.3%, that is, from ¥7,679,869 to ¥5,507,668. Additionally, by switching to generic acyclovir, the cost of medicine would possibly be reduced by 85.0%, that is, from ¥7,679,869 to ¥1,154,055.

Discussion

Although the mean HZ incidence is 4-6 per 1,000 person-years (8, 9), immunocompromised hematological patients, such as those receiving intensive chemotherapy, are at increased risk of HZ. Patients with HZ sometimes suffer

Table III. *Simulation for saving prophylactic medicine costs.*

	Prophylactic medicine		Total*	Rate (%)
	With AVC (N=67)	With VACV (N=42)		
Current costs (¥)	2,869,917	4,809,952	7,679,869	100
Simulation costs 1 (¥)	ACV 2,869,917	VACV → ACV 2,637,751	5,507,668	71.7
Simulation costs 2 (¥)	ACV → ACV (GM) 601,352	VACV → VACV (GM) 2,082,841	2,684,193	35.0
Simulation costs 3 (¥)	ACV → ACV (GM) 601,352	VACV → ACV (GM) 552,703	1,154,055	15.0

ACV, Acyclovir (Zovirax®); VACV, valaciclovir (Valtrex®); GM, generic medicine;¥, Japanese yen. *Calculated with the following costs using Japanese medicine prices of December 2015: ACV (Zovirax®): ¥239.1, ACV (GM): ¥50.1, VACV (Valtrex®): ¥436.0, VACV (GM): ¥188.8 per tablet. The generic medicines were calculated using the cheapest prices available in Japan.

from long-lasting post-herpetic neuralgia, which results in a reduction of quality of life, or a need for RDI by interruption of chemotherapy (10). Several studies have reported high incidences, ranging from 12 to 57%, during bortezomib treatment in patients with MM (11-13), or 8 to 9% during rituximab treatment in patients with NHL (6, 14). Forty-four out of the 573 patients (7.7%) in this study developed HZ. The number of patients with HZ was highest among patients with NHL (28/44, 63.6%), and not so high in those with MM (9/44, 20.5%). The reason for this is that there is evidence of antiviral prophylaxis for patients with MM using bortezomib (1, 2), and it has become general support therapy. Therefore, most of these patients receive antiviral prophylaxis during treatment. When we compared the prophylaxis rate by disease, there was a large difference between those with NHL (39/310, 12.6%) and those with MM (64/100, 64.0%). Considering the treatment risks for developing HZ, 84.1% of patients had received chemotherapy including corticosteroids. Special attention has to be paid to hematological patients treated with corticosteroids. Additionally, 16 patients (16/44, 36.4%) with HZ received rituximab. Although the HZ rate in patients who received rituximab was lower (16/246, 6.5%) than in other reports (6, 7), such patients may need to be administered prophylactic antiviral medicines because of their reduced antibody-mediated immunity.

Numerous reports exist on the prophylactic dose administration of acyclovir. For example, Aoki *et al.* (2) recommended 200 mg once daily and Kim *et al.* (1) recommended 400 mg once daily. Regarding valaciclovir, there are fewer reports, but Fukushima *et al.* (15) recommended 500 mg once daily. In our study, patients received acyclovir prophylaxis orally at a dose of 200 mg daily,or valaciclovir at 500 mg. Valaciclovir is a highly convenient medicine because it is a pro-drug, an esterified version of acyclovir that has greater oral bioavailability than acyclovir (16). For example, valaciclovir is used at 500 mg twice daily instead of 200 mg four times daily for acyclovir to prevent herpes simplex virus infection for patients with hematopoietic stem cell transplantation. In this study, there were 67 patients (67/109, 61.5%) receiving acyclovir and 42 patients (42/109, 38.5%) receiving valaciclovir prophylaxis. Therefore, the use of valaciclovir prophylaxis was high in our hospital. When we compared prophylaxis medicine rates by disease, patients with MM were significantly more frequent than other patients in the acyclovir-treated group. The administration of prophylactic acyclovir for patients with MM who were receiving bortezomib treatment seems to be established. In the valaciclovir-treated group, post-herpetic patients and patients with NHL were significantly more frequent ($p<0.001$).

Only one patient from each of the acyclovir or valaciclovir prophylaxis groups developed HZ (two in total from these groups). The patient in the acyclovir group who developed HZ had MM and received bortezomib, melphalan with predonisolone regimen as first chemotherapy. She developed localized HZ on a finger of her right hand dorsally on day 31 and was treated with a therapeutic dosage of acyclovir for 7 days. After that, she was able to continue chemotherapy. Additionally, the patient who developed HZ in the valaciclovir group had NHL and had received regimens such as rituximab, purine analog, bendamustine, and autologous hematopoietic stem cell transplantation. She developed localized HZ on her right forearm on day 74 of the fourth regimen of rituximab, cyclophospamide, cytarabine, dexamethasoneand etoposide in the eighth chemotherapy round. After that, she was not able to continue treatment.

Although only two patients developed HZ, our results suggest that low-dose acyclovir or valaciclovir prophylaxis could prevent the occurrence of HZ. However, the duration of prophylaxis was long (median=202 days in the acyclovir group, median=143 days in the valaciclovir group), and prophylactic medicine costs became expensive. Therefore, we created a simulation for cost savings. The total prophylactic cost was ¥7,679,869 for 5 years for 109 patients in this study (¥2,869,917 in the acyclovir group and ¥4,809,952 in the

valaciclovir group). There was no difference in efficacy between the two prophylactic medicines, and if we had changed from valaciclovir to the cheaper acyclovir, the medical cost could possibly have been reduced by 28.3%, that is, from ¥7,679,869 to ¥5,507,668. Recently, the use of generic medicines has been recommended in order to reduce medical costs and improve medical insurance financing in Japan. Therefore, changing all prophylactic medicines to the most inexpensive acyclovir generic medicine would possibly reduce them by 85.0%, that is, from ¥7,679,869 to ¥1,154,055. Considering medical prices, we should select the cheaper form of acyclovir.

In conclusion, our data indicate that chemotherapy including corticosteroids is associated with a high incidence of HZ. Although antiviral prophylaxis for patients with MM treated with bortezomib has become general support therapy, we should also administer prophylactic medicines to patients with NHL treated with corticosteroids. Considering the prophylaxis cost, there was no difference in efficacy between acyclovir and valaciclovir, the cheaper acyclovir being useful for HZ prophylaxis. To our knowledge, there are no reports indicating generic medicine of acyclovir for HZ prophylaxis. Consequently, we believe that prospective studies with a generic medicine are necessary to establish the efficacy of cheap prophylaxis.

Conflicts of Interest

The Authors declare they have no conflicts of interest.

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