Clinical Hematology International
Vol. **1(2)**, June 2019, *pp.* 101–104
DOI: https://doi.org/10.2991/chi.d.190329.001; eISSN: 2590-0048
https://www.atlantis-press.com/journals/chi/

Research Article

Low-Dose Acyclovir Prophylaxis for *Varicella zoster* Reactivation in Autologous Hematopoietic Cell Transplantation Recipients

Naomi Fei[1,*], Nilay Shah [2], Aaron Cumpston[2,3], Sijin Wen[4], Kelly G. Ross[2], Michael Craig[2], Abraham S. Kanate[2]

[1]*Section of Hematology and Oncology, West Virginia University, Morgantown, WV, USA*
[2]*Alexander B. Osborn Hematopoietic Malignancy and Cellular Therapy Program, West Virginia University, Morgantown, WV, USA*
[3]*Department of Pharmacy, West Virginia University Hospitals, Morgantown, WV, USA*
[4]*Department of Biostatistics, School of Public Health, West Virginia University, Morgantown, WV, USA*

ARTICLE INFO

Article History
Received 17 Feb 2019
Accepted 28 Mar 2019

Keywords
Autologous hematopoietic cell transplantation
Varicella zoster virus
Acyclovir
Valacyclovir

ABSTRACT

Varicella zoster virus (VZV) reactivation after autologous hematopoietic cell transplantation (auto-HCT) may be observed in a quarter of patients. Currently, prophylactic use of acyclovir 800 mg twice daily or valacyclovir 500 mg twice daily is recommended for prophylaxis against VZV reactivation for at least one-year post-HCT, with continued use recommended in immunosuppressed recipients. Acyclovir dosing regimens vary between institutions despite the noted recommendations. In this single-center, retrospective study, recipients of auto-HCT who received at least one year of low-dose antiviral prophylaxis defined as the equivalent of acyclovir 400 mg orally twice daily or valacyclovir 500 mg daily were included. The primary objective of this study was to assess the incidence of VZV reactivation with low-dose acyclovir/valacyclovir prophylaxis in autograft recipients. One hundred and eighty patients undergoing auto-HCT between April 2008 and March 2015 were included. Patients received low-dose acyclovir, for a median duration of 55.5 months (range 12–100). There were no occurrences of VZV reactivation while patients were on these drugs. However, 2 patients (1.1%) had VZV reactivation after discontinuation of therapy, occurring 18.8 and 14 months from transplant and 6.7 and 2 months after stopping prophylaxis, respectively. Our retrospective analysis found low-dose antiviral prophylaxis with oral acyclovir 400 mg twice daily or valacyclovir 500 mg daily to be effective in preventing VZV reactivation in auto-HCT recipients.

1. INTRODUCTION

For recipients of autologous hematopoietic cell transplantation (auto-HCT), *Varicella zoster* virus (VZV) reactivation may be observed in 16–28% of patients [1]. This may cause significant morbidity, and clinically presents as dermatomal lesions, cutaneous dissemination, visceral dissemination, postherpetic neuralgia, neurologic dysfunction, bacterial superinfection, and, rarely, death. In >90% of cases, VZV reactivation occurs within the first year of HCT [1–5]. Current consensus guidelines recommend VZV prophylaxis in the posttransplant period with acyclovir 800 mg twice daily (BID), or its prodrug, valacyclovir, 500 mg BID, for at least one-year post-HCT [6]. While most centers implement VZV prophylaxis for this period, significant institutional variations regarding administered dosages have been reported [7,8]. Prior studies evaluating acyclovir ranging from 200 mg BID to 800 mg BID have shown varying rates of VZV reactivation after allogeneic HCT [9–13]. Erard *et al.* reported favorable VZV reactivation incidence (<1%) with acyclovir 800 mg BID or valacyclovir 500 mg BID for one-year after allogeneic HCT. Our group previously reported a 2% VZV reactivation rate in auto-HCT patients receiving one year of prophylaxis ($n = 40$) with acyclovir 400 mg BID or valacyclovir 500 mg daily [7]. Extension in duration of antiviral prophylaxis is recommended by the 2009 Centers for Disease Control (CDC) guidelines for those patients who are immunosuppressed [6]. There are, however, limited data evaluating the long term (>1 year) use of antiviral prophylaxis [12,14]. One study reported no VZV reactivations with 24 months ($n = 22$) of post-HCT valacyclovir 1000 mg BID [14].

The current study evaluates the efficacy of low-dose acyclovir (LD-ACV) 400 mg BID or valacyclovir 500 mg daily in a larger cohort of patients after auto-HCT. In addition, we describe the utilization and effect of LD-ACV in select patients who received greater than one year of prophylaxis.

2. PATIENTS AND METHODS

2.1. Patient Population

In this single-center, retrospective study, recipients of auto-HCT between April 2008 and March 2015 who received at least one

Corresponding author. 4th Floor HSCN Rm 4071, 1 Medical Center Drive, Morgantown West Virginia. Phone: 304-282-0165, *Email: nhfei@hsc.wvu.edu*
Peer review is under the responsibility of IACH
Data availability statement: The data that support the findings of this study are available from the corresponding author, upon reasonable request.

year of antiviral prophylaxis were included. Only adult patients (>18 years) with documented follow-up for at least one year after autologous transplant or until documented VZV reactivation were included in this study. All patients received LD-ACV, defined as the equivalent of acyclovir 400 mg BID or valacyclovir 500 mg daily, as standard prophylaxis, based on institutional guidelines. The prophylactic doses of acyclovir and valacyclovir were developed as institutional standard in 2008, prior to the current published standards, and were, in essence, based on recommended *Herpes simplex* virus dosing algorithms [15].

The primary objective of this study was to assess the incidence of VZV reactivation with LD-ACV prophylaxis in auto-HCT recipients, including assessment for VZV reactivation up to one year after discontinuation of LD-ACV prophylaxis. A subset of patients who received LD-ACV prophylaxis for >1 year after auto-HCT, as clinically deemed appropriate by the treating physician, were also evaluated separately to assess its efficacy. Clinical characteristics of patients who developed *Herpes zoster* infection were described in detail (Table 2).

2.2. VZV Diagnosis and Definitions

The diagnosis of VZV reactivation was clinical, based on presenting symptoms and signs of *Herpes zoster* infection. Localized cutaneous reactivation was defined as the appearance of typical cutaneous vesicular lesions limited to two or less adjacent dermatomes. Disseminated cutaneous reactivation was diagnosed if cutaneous vesicular lesions extended to three or more dermatomes. Viscerally disseminated reactivation with organ involvement was confirmed by positive direct immunofluorescence assay or by positive polymerase chain reaction of specimens obtained from affected tissues/organs [2]. Postherpetic neuralgia was defined as persistent pain at the site of prior cutaneous lesion involvement for >3 months after resolution of lesions [2–5]. Alternative complications screened for included cutaneous scarring, motor, and sensory deficits at the site of prior cutaneous lesions, and hospitalization secondary to VZV-related treatment.

2.3. Statistical Analysis

Patient characteristics were analyzed using descriptive statistics. Categorical data were described using contingency tables, including counts and percentages. Continuously scaled measures were summarized by mean with standard deviation or median with range. Fisher's exact test and Wilcoxon rank sum test were used to assess the difference/balance of categorical and continuous variables between patients who received standard duration *versus* extended duration, respectively. Response rates were estimated based on the binomial distribution and were compared using Fisher's exact test. A p value < 0.05 for the difference was considered significant. Statistical analyses were carried out using software R (version 3.31, R Foundation, Vienna, Austria) and SAS 9.1 (SAS Institute, Cary, NC).

3. RESULTS

3.1. Baseline Characteristics

Consecutive patients undergoing auto-HCT between April 2008 and March 2015 ($n = 235$) at the West Virginia University Hospitals were considered for this study. Fifty-five patients were excluded for various reasons including (i) enrollment in inactivated VZV vaccination study (NCT01229267; $n = 19$), (ii) receiving less than 365 days of prophylaxis ($n = 27$), and (iii) having less than one year of follow-up after auto-HCT ($n = 9$).

In the final analysis, 180 patients receiving LD-ACV and followed in clinic for at least one year after auto-HCT were included. The median follow-up from date of auto-HCT was 31 months (range 12–100). Table 1 describes the baseline clinical and transplant characteristics of the patients included in this study. Briefly, the cohort's median age was 58 (range 21–74), and it was mainly comprised of men (61%) with a diagnosis of multiple myeloma (66%). The majority of patients received peripheral blood autografts (99%), and were in complete remission (76%) at the time of transplant. Thirty-two patients had died at the time of last follow-up, with primary disease being the main cause of death ($n = 21$). Among the 75 patients (42%) who relapsed after the auto-HCT, 73% ($n = 55$) had multiple myeloma and 27% ($n = 20$) had non-Hodgkin lymphoma.

Extended duration LD-ACV prophylaxis (>12 months) was given to 71 patients, as clinically indicated by the treating physician. Compared to those receiving standard duration (<12 months), patients with extended prophylaxis were more likely to have received prior bortezomib (40% *versus* 77.4%, $p < 0.001$), prior radiation (13% *versus* 34%, $p = 0.001$), and more likely to have been on antiviral prophylaxis prior to auto-HCT (36% *versus* 77%, $p < 0.001$).

Table 1 | Baseline clinical and transplant characteristics of the patients.

	***N* = 180**	**%**
Male	110	61
Median age at transplant (range)	58 (21–74)	
ECOG performance status >2	23	13
Diagnosis		
Multiple myeloma	119	66
Non-Hodgkin lymphoma	42	23
Hodgkin lymphoma	18	10
Amyloidosis	1	0.5
Pretransplant treatment history		
Proteasome inhibitors	99	55
Radiation therapy	38	21
Pretransplant antiviral use	94	52
Pretransplant remission status		
Complete remission	62	34
Partial remission	98	54
Stable disease	10	5.5
Progressive disease	10	5.5
Conditioning regimen		
Melphalan	122	68
Carmustine/etoposide/ cyclophosphamide	58	32
Graft source		
Peripheral blood	179	99
Bone marrow	1	0.5
Response to transplant		
Complete remission	136	75.5
Partial remission	29	16
Refractory disease	15	8
Posttransplant relapse/progression	75	42
Number of deaths	32	18
Cause of death		
Infection	3	2
Primary disease	21	12
Unknown	8	4

Abbreviations: ECOG: Eastern Cooperative Oncology Group.

Table 2 | Characteristics of *Varicella zoster* virus reactivation.

	Case 1	Case 2
Patient age, gender	64-year-old, female	72-year-old, male
Oncologic diagnosis	Diffuse large B-cell lymphoma	Multiple myeloma
Response to autologous transplant	Progressive disease	Complete remission
Time from transplant to reactivation	565 days	427 days
Time from antiviral discontinuation to reactivation	200 days	62 days
Reactivation type	Localized cutaneous, T10 dermatome	Localized cutaneous, L2 dermatome
Complications of Reactivation	Postherpetic neuralgia	Postherpetic neuralgia
Hospitalization	No	No

3.2. VZV Reactivation and Complications of Disease

The VZV reactivation rate in the entire cohort was 2/180 (1.1%). The two cases of VZV reactivation were noted in patients who received one year of LD-ACV but after discontinuation of prophylaxis (Table 2). Both were >60 years of age, but were of differing genders and underlying oncologic diagnoses (multiple myeloma and diffuse large B-cell lymphoma). The clinical presentations of both reactivations were similar, as cutaneous lesions localized to one dermatome, which resolved with only postherpetic neuralgia as a lasting complication. No disseminated forms of VZV reactivation were noted. Among the 71 patients who received extended-duration prophylaxis, no documented VZV reaction was identified. No attributable adverse effects related to LD-ACV therapy was noted in our patient cohort. Incidentally, no cases of documented *Herpes simplex* virus reactivation were noted in the study cohort either.

4. DISCUSSION

Reactivation of VZV has been reported in up to a quarter of recipients of high-dose therapy and auto-HCT, with a potential for severe morbidity and complications [1]. Acyclovir and its prodrug valacyclovir have been used for prophylaxis against VZV reactivation in the posttransplant period [6]. Initial recommendations regarding duration of acyclovir prophylaxis were conservative (approximately three months post-HCT) due to concerns for rebound reactivation [16,17]. Subsequent studies using oral acyclovir or valacyclovir for one year after transplant did not observe a disproportionate increased of VZV reactivation after cessation of prophylaxis [12]. In 2009, the CDC guidelines supported the use of acyclovir prophylaxis for one year after HCT, and its continued usage if the patient remained immunosuppressed [6].

While recommendations regarding duration of prophylaxis have been published, dosing regimens continue to vary between institutions. Prior studies have used oral acyclovir 800 mg twice daily for VZV prophylaxis, with findings of a 5.8% reactivation rate at one year, compared to 20.4% in those without prophylaxis [12]. A similar dosing regimen of oral acyclovir 800 mg twice daily resulted in no reactivation cases at one year compared to 10.3% in those with placebo [11]. In the postallogeneic transplant population, acyclovir at 400 mg daily as a single dose or in two divided 200-mg doses resulted in 10% and 4.5% VZV reactivation, respectively [9,13]. Therefore, based on available data, mostly in allogeneic HCT patients, no clear correlation exists between the dose of acyclovir and the rate of reactivation.

Our current study is the largest to date evaluating a low-dose antiviral prophylaxis approach. We assessed the VZV reactivation rates after auto-HCT with LD-ACV in 180 patients and noted only 2 cases (1.1%). It is noteworthy that both instances of reactivation were localized to the skin, with only postherpetic neuralgia as a reported complication. Importantly, no cases of breakthrough reactivation (while on prophylaxis) were noted for patients while on LD-ACV or after discontinuation. We previously reported a 2% VZV reactivation with LD-ACV prophylaxis (n = 40) for one year after auto-HCT [7]. The current data in a larger patient cohort (n = 180) suggest that LD-ACV prophylaxis administered for one year after auto-HCT would be sufficient to prevent VZV reactivation.

The efficacy of LD-ACV prophylaxis when used for greater than one-year postauto-HCT was also examined. In the subgroup of patients who received greater than one year of LD-ACV, neither were any cases of VZV reactivations noted, nor were any attributable adverse effects related to extended use of LD-ACV reported. This suggests that the continued use of LD-ACV prophylaxis beyond one-year post-HCT is probably safe and effective. Interestingly, the 71 patients who received longer LD-ACV were more likely to have received pre-HCT bortezomib/radiation therapy and less likely to have achieved a complete remission after auto-HCT, likely necessitating additional chemotherapy. It is possible that more patients in this group required further systemic therapy, thus being deemed "immunocompromised" and necessitating continued VZV prophylaxis.

This study was limited by its retrospective nature. Data regarding VZV incidence were collected via retrospective chart review and, therefore, patients with reactivations who were not recorded in the hospital database may not have been captured. VZV serologies were not collected in patients prior to transplant, therefore the assumption of zoster reactivation rather than primary infection was assumed due to the high prevalence of positive VZV serology in the population. Notwithstanding these limitations, in conclusion, this study confirms the effectiveness of LD-ACV defined as oral acyclovir 400 mg BID or valacyclovir 500 mg daily for prevention of VZV reactivation in auto-HCT recipients. The prophylactic LD-ACV was effective in those requiring extended duration prophylaxis with no breakthrough reactivations noted.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS

N.F., N.S., A.C., S.W., K.R., M.C. and A.K. contributed to the design and implementation of the research, to the analysis of the results and to the writing of the manuscript.

ACKNOWLEDGMENTS

This research was supported in part by ACS 16-143-07-IGR from the American Cancer Society (S WEN).

REFERENCES

[1] Shuchter, LM, Wingard, JR, Piantadosi, S, Burns, WH, Santos, GW, Saral, R. Herpes zoster infection after autologous bone marrow transplantation. Blood 1989;74(4);1424–7.

[2] Sampathkumar, P, Drage, LA, Martin, DP. Herpes zoster (shingles) and postherpetic neuralgia. Mayo Clin Proc 2009;84(3);274–80.

[3] Onozawa, M, Hashino, S, Haseyama, Y, *et al*. Incidence and risk of postherpetic neuralgia after varicella zoster virus infection in hematopoietic cell transplantation recipients: Hokkaido hematology study group. Biol Blood Marrow Transplant 2009;15;724–9.

[4] Arvin, AM. Varicella-zoster virus: pathogenesis, immunity and clinical management in hematopoietic cell transplant recipients. Biol Blood Marrow Transplant 2000;6;219–30.

[5] Han, CS, Miller, W, Haake, R. Varicella zoster infection after bone marrow transplantation: incidence, risk factors and ocmplications. Bone Marrow Transplant 1994;13;277–83.

[6] Tomblyn, M, Chiller, T, Einsele, H, Gress, R, Sepkowitz, K, Storek, J, *et al*. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. Biol Blood Marrow Transplant 2009 Oct;15(10);1143–238.

[7] Truong, Q, Veltri, L, Kanate, A, Craig, M, Hamadani, M, Cumpston, A, Hu, Y. Impact of the duration of antiviral prophylaxis on rates of varicella-zoster virus reactivation disease in autologous hematopoietic cell transplantation recipients. Ann Hematol 2014;93;677–82.

[8] Trifilio, S, Mehta, J. Antimicrobial prophylaxis in hematopoietic stem cell transplantation recipients: 10 years after. Transpl Infect Dis 2014;16(4);548–55.

[9] Kanda, Y, Mineishi, S, Saito, T, Saito, A, Yamada, S, Ohnishi, M. Long-term low-dose acyclovir against varicella-zoster virus reactivation after allogeneic hematopoietic stem cell transplantation. Bone Marrow Transplant 2001;28;689–92.

[10] Thomson, KJ, Hart, DP, Banerjee, L, Ward, KN, Peggs, KS, *et al*. The effect of low dose acyclovir on reactivation of varicella zoster virus after allogeneic haemopoietic stem cell transplantation. Bone Marrow Transplant 2005 Jun;35(11);1065–9.

[11] Boeckh, M, Kim, HW, Flowers, ME, Meyers, JD, Boden, RA. Long-term acyclovir for prevention of varicella zoster virus disease after allogeneic hematopoietic cell transplantation – a randomized double-blind placebo-controlled study. Blood 2006;107(5);1800–5.

[12] Erard, V, Guthrie, KA, Varley, C, Heugel, J, Wald, A, Flowers, ME, *et al*. 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 2007;110(8);3071–7.

[13] Kawarmura, K, Wada, H, Yamasaki, R, Ishihara, Y, *et al*. Prophylactic role of long-term ultr-low-dose acyclovir for varicella zoster virus disease after allogeneic hematopoietic stem cell transplantation. Int J Infect Dis 2014;19;26–32.

[14] Klein, A, Miller, KB, Sprague, K, DesJardin, JA, Snydman, DR. A randomized, double-blind, placebo-controlled trial of valacyclovir prophylaxis to prevent zoster recurrence from months 4 to 42 after BMT. Bone Marrow Transplant 2011;46;294–9.

[15] CDC, IDSA, ASBMT. Guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. MMWR Recomm Rep 2000 Oct;49(RR-10);1–125, CE1–7.

[16] Sempere, A, Sanz, GF, Senent, L, de la Rubia, J, *et al*. Long-term acyclovir prophylaxis for prevention of varicella zoster virus infection after autologous blood stem cell transplantation in patients with acute leukemia. Bone Marrow Transplant 1992;10;495–8.

[17] Ljungman, P, WIlczek, H, Gahrton, G, Gustavsson, A, *et al*. Long term acyclovir prophylaxis in bone marrow transplant recipients and lymphocyte proliferation responses to herpes virus antigens in vitro. Bone Marrow Transplant 1986;1;185–92.