Long-term ultra-low-dose acyclovir against varicella-zoster virus reactivation after allogeneic hematopoietic stem cell transplantation

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To evaluate the efficacy of long-term prophylaxis with ultra-low-dose acyclovir against varicella-zoster virus (VZV) reactivation, we analyzed the records of 242 Japanese adult patients who underwent allogeneic hematopoietic stem cell transplantation for the first time from 1995 to 2006 at our hospital. We started long-term oral acyclovir at 200 mg/day in July 2001. Acyclovir was continued until the end of immunosuppressive therapy and at least 1 year after transplantation. Sixty-six patients developed VZV reactivation at a median of 248 days after HSCT, with a cumulative incidence of 34.7%. Only one breakthrough reactivation occurred during long-term acyclovir, which responded well to therapeutic dose of valacyclovir. The use of long-term acyclovir was the only independent determinant that significantly decreased the overall incidence of VZV reactivation (20% vs. 50%, $P < 0.0001$). With this prophylaxis, visceral dissemination and serious complications other than post-herpetic neuralgia was completely eliminated, and thereby need for hospitalization was significantly reduced (21% vs. 71%, $P = 0.0034$). Fifteen of the 57 patients who discontinued acyclovir developed VZV reactivation, with a cumulative incidence of 32.1%. VZV reactivation following discontinuation tended to occur in patients who were receiving immunosuppressive therapy at the cessation of acyclovir. These findings suggested that long-term prophylaxis of ultra-low-dose acyclovir resulted in a successful prevention of severe VZV-related symptoms and death, with a significantly decreased overall incidence of VZV reactivation. Prolongation of prophylactic acyclovir on profound immunosuppression might be important for thorough suppression of VZV reactivation. Am. J. Hematol. 83:472–476, 2008.

Introduction

Varicella-zoster virus (VZV) infection remains a common complication after hematopoietic stem cell transplantation (HSCT) [1–4]. VZV infection develops as a reactivation of latent virus mainly between the third and twelfth month after transplantation, with a cumulative incidence of more than 30% [1,2]. Localized dermatomal rash is the most common clinical presentation, whereas dissemination or visceral involvement is occasionally observed, leading to a fatal outcome. Although most of VZV infections were successfully treated with antiviral agents, VZV-related complications including post-herpetic neuralgia and secondary infection significantly affect the patient's quality of life [1,5].

The introduction of long-term prophylaxis with low-dose acyclovir against VZV reactivation has therefore been investigated [4,6–10]. Several studies concluded that prophylactic acyclovir at 600–3,200 mg/day continued for a fixed period up to 6 months or 1 year have failed to decrease the overall incidence of VZV reactivation [4,6–8]. Despite that VZV reactivation during prophylaxis was significantly reduced, a substantial number of VZV reactivation occurred following the discontinuation of acyclovir. A most recent randomized placebo-controlled trial showed a predominant occurrence of VZV reactivation after the cessation of acyclovir, which was given at 800 mg/day for 1 year after HSCT, in recipients with prolonged immunosuppression [8]. Moreover, other studies reported that long-term acyclovir at 400 mg/day continued until the end of immunosuppressive therapy could not suppress VZV reactivation after the discontinuation of acyclovir [9,10]. Thus, the appropriate prophylactic dose and duration of acyclovir to decrease the overall incidence of VZV reactivation have not been clarified.

We carried out a novel trial of long-term acyclovir prophylaxis at an ultra-low-dose (200 mg/day) until the end of immunosuppressive therapy and at least 1 year after HSCT, and retrospectively compared the incidence of VZV reactivation with historical control patients who did not receive long-term prophylaxis. With this prophylaxis, lower-cost, less side effects, and better compliance may also be promising.

Results

Incidence and risk factors for VZV reactivation after HSCT

In total of 242 patients, 137 received long-term acyclovir following prophylaxis against HSV infection, whereas the remaining 105 did not receive long-term acyclovir. Overall, 66 out of the 242 patients developed VZV reactivation at a median of 248 days (range 50–1,494 days) after HSCT,

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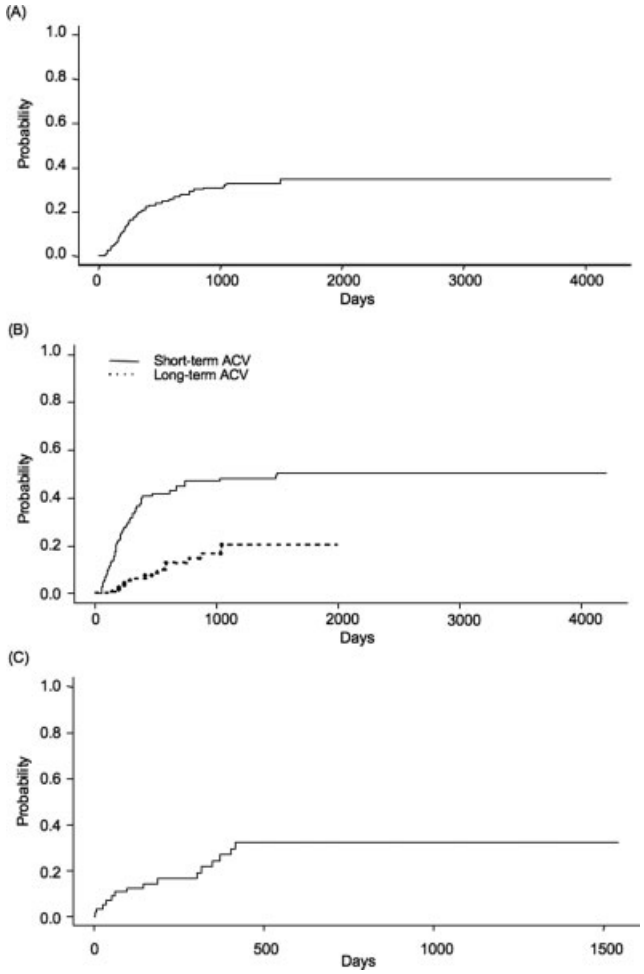

Figure 1. (A) Cumulative incidences of VZV reactivation after HSCT in all 242 patients. (B) Cumulative incidences of VZV reactivation after HSCT in 137 patients who received long-term acyclovir versus 105 patients who did not. (C) Cumulative incidences of VZV reactivation after the cessation of long-term acyclovir in 57 eligible patients for analysis.

TABLE I. Risk Factors for VZV Reactivation After HSCT

Factors	Variables	n	Incidence (%)	*P*-value
Univariate analysis				
Age	≥ 40 years old	117	25	0.005
	<40 years old	125	43	
Sex	Male	154	34	0.71
	Female	88	37	
Disease risk	Standard-risk	96	38	0.63
	High-risk	146	32	
Graft source	Bone marrow	166	40	0.06
	Peripheral blood	73	25	
Donor type	Matched sibling donor	97	40	0.11
	Alternative donor	145	31	
Regimen (1)	Conventional	204	37	0.05
	Reduced-intensity	38	25	
Regimen (2)	TBI regimen	179	36	0.63
	Non-TBI regimen	63	32	
Long-term ACV	Yes	137	20	<0.0001
	No	105	50	

Factors	Variables	*n*	Relative risk 95% CI	*P*-value
Grade II–IV acute GVHD	Yes	97	1.18 (0.72–1.94)	0.51
	No	145		
Chronic GVHD	Yes	131	0.87 (0.51–1.50)	0.62
	No	76		

Factors	Relative risk	95% CI	*P*-value
Multivariate analysis			
Long-term ACV	0.23	0.13–0.39	<0.0001

with a cumulative incidence of 34.7% (Fig. 1A). Only one patient experienced a breakthrough reactivation during long-term acyclovir, which responded promptly to a therapeutic dose of valacyclovir. In univariate analyses, younger age, bone marrow transplantation, conventional regimen, and the use of long-term acyclovir were significantly associated with the low VZV reactivation incidence rate (Table I). In a multivariate analysis, the use of long-term acyclovir was identified as the only independent factor that significantly decreased the incidence of VZV reactivation (20% vs. 50%, $P < 0.0001$, Table I, Fig. 1B).

Clinical features of patients who developed VZV reactivation

Fifty-three of the 66 VZV reactivations (80%) occurred in a localized dermatomal distribution (Table II). Clinically significant complications developed in 17 patients, the most common of which was post-herpetic neuralgia. Among these complications, only post-herpetic neuralgia was seen in three patients with long-term acyclovir, whereas serious complications including CNS involvement, motor neuropathy, and ophthalmic complications were involved in the remaining 14 patients without long-term acyclovir.

Fifty-two of the 66 patients developed VZV reactivation in outpatient setting. Among these patients, hospitalization was required for VZV reactivation in 3 of 14 patients with long-term acyclovir and in 27 of 38 patients without long-term acyclovir (21% vs. 71%, $P = 0.0034$).

Seven of the 66 patients with VZV reactivation (11%) developed recurrent VZV reactivation in the different dermatome, at a median of 95 days (range 55–798 days) after the first episode. All of them never received acyclovir after finishing the treatment for the first episode. At the time of recurrence, five of the seven patients were receiving immunosuppressive therapy and the remaining two showed severe lymphocytopenia less than 300/μl due to chemotherapy for relapse of hematological malignancy. The third episode of VZV reactivation occurred in two patients, at 158 and 240 days after the second reactivation. None was receiving acyclovir at the time of second or third VZV reactivation. All the patients responded well to treatment with antiviral agents, and none of them directly died of VZV reactivation.

Incidence and risk factors for VZV reactivation after the cessation of long-term acyclovir

Of 137 patients who received long-term acyclovir, 73 patients were receiving acyclovir until VZV reactivation, their last follow-up, or death. The other seven died within a week following the discontinuation of acyclovir. Therefore, 80 patients were excluded and only 57 patients were eligible for analysis after the cessation of acyclovir. The median follow-up duration from the discontinuation of acyclovir was 279 days (range 9–1,936 days). They received long-term acyclovir with a median prophylactic period of 358 days (range 49–1,259 days). Fifteen patients developed VZV reactivation at a median of 147 days (range 5–415 days)

TABLE II. Clinical Presentation and Secondary Complications of VZV Reactivation

Low-dose ACV	No	Yes	Total
Total patients	105	137	242
VZV reactivation	50	16	66
Out-patient onset	38	14	52
Hospitalized	27	3	30
Treated as outpatient	11	11	22
Valacyclovir	4	8	12
Acyclovir	7	3	10
Clinical presentations			
Localized	39	14	53
Trigeminal	4	2	6
Cervical	5	1	6
Thoracic	22	5	27
Lumbar	5	4	9
Sacral	3	2	5
Disseminated	11	2	13
Cutaneous	7	2	9
Visceral	4	0	4
Complications	14	3	17
Ophthalmic complications	1	0	1
Motor neuropathy	1	0	1
CNS involvement	3*	0	3
Post-herptic neuralgia	9	3	12

*One patient had both CNS involvement and post-herpetic neuralgia.

TABLE III. Risk Factors for VZV Reactivation After the Cessation of Long-Term ACV

Factors	Variables	*n*	Incidence(%)	*P*-value
Univariate analysis				
Age	≥40 years old	31	34	0.56
	<40 years old	26	29	
Sex	Male	36	21	0.14
	Female	21	54	
Disease risk	Standard-risk	26	30	0.39
	High-risk	31	34	
Graft source	Bone marrow	28	34	0.96
	Peripheral blood	28	41	
Donor type	Matched sibling donor	23	29	0.61
	Alternative donor	34	34	
Regimen (1)	Conventional	43	32	0.94
	Reduced-intensity	14	31	
Regimen (2)	TBI regimen	42	30	0.57
	Non-TBI regimen	15	38	
Duration of long-term ACV	<1 year	33	30	0.85
	≥1 year	24	33	
Immunosuppressive therapy at the cessation of ACV	Yes	25	44	0.12
	No	32	20	

Factors	Variables	*n*	Relative risk 95% CI	*P*-value
Chronic GVHD	Yes	37	1.68	0.47
	No	17	(0.40–6.99)	

after the discontinuation of acyclovir, with a cumulative incidence of 32.1% (Fig. 1C). Although statistically significant risk factors were not identified to affect the incidence of VZV reactivation after discontinuation, ongoing immunosuppressive therapy at the cessation of acyclovir tended to increase the incidence of VZV reactivation (Table III).

Discussion

This study demonstrated that the long-term prophylactic acyclovir at 200 mg/day was highly effective to reduce VZV reactivation, dissemination and serious complications, as well as VZV-related mortality in HSCT recipients. There was only one breakthrough of localized reactivation that responded well to the therapeutic dose of valacyclovir. A once-a-day dosing of 200 mg until the cessation of immunosuppressive therapy and at least 1 year after HSCT significantly decreased the overall incidence of VZV reactivation from 50 to 20%, in contrast with the previous studies in which various doses of 600 mg/day or more were given for a fixed period up to 6 months or 1 year after HSCT without significant reduction of the overall incidence of VZV reactivation [4,6–8]. Although an optimal prophylactic dose and duration of acyclovir administration has not been clarified, this extended prophylactic approach to continue acyclovir until the end of immunosuppressive therapy and at least 1 year after HSCT may be more appropriate than the shorter prophylaxis or fixed-duration prophylaxis. Also, this is the first report that the ultra-low-dose of acyclovir at only 200 mg/day was sufficient to prevent VZV reactivation during prophylaxis.

In this study, however, VZV reactivation was not uncommon after the discontinuation of long-term acyclovir, as previously observed in the other two studies in which acyclovir at 400 mg/day was given until the end of immunosuppressive therapy [9,10]. Nevertheless, the severity of clinical symptoms was ameliorated and thereby need for hospitalization was markedly reduced by the long-term acyclovir. Among the 15 patients who developed VZV reactivation after the cessation of acyclovir, none showed visceral dissemination or serious complications. The less severe symptoms in patients with long-term acyclovir may reflect the contribution of VZV-specific immune recovery, which might have been accelerated by subclinical VZV reactivation. It has been shown that *in vivo* re-exposure to VZV antigens without clinical symptoms may boost immunity and thereby prevent subsequent symptomatic VZV reactivation [11]. Lower daily dosing of 200 mg might have permitted subclinical VZV reactivation to establish the reconstitution of VZV-specific immunity. There is another possibility that need for hospitalization in patients with long-term acyclovir might have been reduced by the use of valacyclovir, which became available from October 2000 in Japan. However, mild cases of VZV reactivation had been treated with oral acyclovir, and actually 7 of 11 patients who developed VZV reactivation without long-term acyclovir were successfully treated with oral acyclovir without hospitalization. Therefore, we suppose that a decreased hospitalization rate in patients with long-term acyclovir was due to less severe symptoms rather than the availability of valacyclovir.

In some patients, long-term acyclovir was discontinued within a year at the physician's discretion or at the request of the patients. This is a limitation of this study, but it revealed that ongoing immunosuppressive therapy at the cessation of acyclovir tended to be more frequently associated with VZV reactivation following discontinuation, which agreed with the conclusion of Boeckh's study that VZV reactivation predominantly occurred in patients with continued systemic immunosuppression [8]. They did not find any significant difference in the reconstitution of VZV-specific immunity between the acyclovir and placebo groups following the 1-year prophylaxis at 800 mg/day. In addition, the study with long-term acyclovir at 400 mg/day also showed that VZV reactivation after the cessation of acyclovir was observed only in patients who were receiving resumed immunosuppressants [10]. In this study, three patients with long-term acyclovir experienced dissemination and/or post-

herpetic neuralgia, all of whom were receiving prolonged immunosuppressive therapy for chronic GVHD both at the cessation of acyclovir and at the time of VZV reactivation. These findings suggest that VZV reactivation as well as the severity of symptoms is strongly related to the decline in VZV-specific immunity as a result of HSCT and/or immunosuppressive therapy. Therefore, continuing acyclovir in patients with profound immunosuppression is recommended for further prevention of VZV reactivation. Another possible approach is to administer inactivated VZV vaccine at the discontinuation of acyclovir [12].

In conclusion, this study showed that the long-term prophylaxis with ultra-low-dose acyclovir might be an effective strategy for the suppression of VZV reactivation during prophylaxis and minimizing the long-term risks of VZV-related complications and mortality. Further investigation is necessary to evaluate the validity of resuming acyclovir for patients with resumed immunosuppressive therapy.

Patients and Methods

Study population

A total of 271 consecutive adult patients ($\geq$16 years old) underwent allogeneic HSCT for the first time at the University of Tokyo Hospital between June 1995 and November 2006. Five patients who died within 35 days after HSCT were excluded, and clinical data for this study were available for 242 of the remaining 266 patients. A median follow-up was 486 days (range, 37–4,209 days) from HSCT for the entire cohort of 242 patients. Thirty-eight patients who received reduced-intensity conditioning were included. The patient characteristics are summarized in TABLE IV. Ninety-seven, 42 and 103 patients received graft from an HLA-matched sibling donor, a mismatched related donor, and a matched unrelated donor, respectively. Unrelated HSCT was performed exclusively using bone marrow, whereas 73 out of 139 related donors chose to donate peripheral blood stem cell graft. Acute leukemia in first remission, chronic myelogenous leukemia in first chronic phase, myelodysplastic syndrome with refractory anemia or refractory anemia with ringed sideroblasts, and aplastic anemia were defined as low-risk diseases, while others were considered high-risk diseases. Donors other than HLA-matched sibling donors were defined as alternative donors.

TABLE IV. Patients' Characteristics

Characteristic		Total patients
Sex (male/female)		154/88
Age, median (range)		39 (16–66)
Underlying disease	Acute leukemia	121
	CML	50
	MDS	26
	NHL/ATL	25
	SAA	10
	Other	10
Graft source	PBSC	73
	BM	166
	CB	3
Donor type	Matched sibling	97
	Mismatched related	42
	Unrelated	103
VZV seropositivity	Positive	231
	Negative	3
	Not examined	8
Preparative regimen	Cy (Etp)/TBI-based regimens	167
	Bu/Cy-based regimens	37
	ATG-based regimens for SAA	7
	Flu-based RIC	31
GVHD prophylaxis	CsA + MTX	200
	Tacrolimus + MTX	18
	Alemtuzumab + CsA + MTX	24
Acute GVHD	Grade 0–I	145
	Grade II–IV	97
Chronic GVHD	Extensive	86
	Limited	45
	None	76

VZV indicates varicella zoster virus; CML, chronic myelogenous leukemia; MDS, myelodysplastic syndrome; NHL, non-Hodgkin's lymphoma; ATL, adult T-cell leukemia/lymphoma; SAA, severe aplastic anemia; PBSC, peripheral blood stem cell; BM, bone marrow; CB, cord blood; Cy, cyclophosphamide; Etp, etoposide; TBI, total body irradiation; Bu, busulfan; ATG, antihymocyte globulin; Flu, fludarabine; RIC, reduced intensity conditioning; GVHD, graft-versus-host disease; CsA, cyclosporine; MTX, methotrexate.

Transplantation procedure

The conventional preparative regimen for leukemia/lymphoma was mainly performed with either total body irradiation (TBI) regimen (cyclophosphamide (Cy) at 60 mg/kg for 2 days and TBI at 2 Gy twice daily for 3 days) or non-TBI regimen (Cy at the same dose combined with busulfan (Bu) at 4 mg/kg for 4 days). In TBI regimen, the dose of Cy was decreased to 40 mg/kg for 1 day and etoposide at 20 mg/kg for 2 days was added instead in patients with impaired cardiac function. Fludarabine (Flu)-based regimens included FB regimen (Flu at 30 mg/m^2 for 6 days and Bu at 4 mg/kg for 2 days) with or without TBI at 4 Gy, FB16 regimen (Flu at the same dose with Bu at 4 mg/kg for 4 days), FM regimen (Flu 30 mg/m^2 for 5 days and melphalan at 140 mg/m^2 for 1 day), and FC regimen (Flu at 25 mg/m^2 for 5 days and Cy at 60 mg/kg for 2 days) were used as reduced-intensity regimens for elderly or clinically infirm patients [13]. Gemcitabine at 1,000 mg/kg/m^2 for 3 days was added to the FB regimen for patients with pancreatic cancer [14]. The conditioning regimen for aplastic anemia was either a rabbit antithymocyte globulin (ATG) regimen (Cy at 50 mg/kg for 4 days and ATG at 5 mg/kg for 5 days with or without TBI at 4 Gy) or an alemtuzumab regimen (Cy at 25 mg/kg for 4 days and Flu at 30 mg/kg for 4 days combined with alemtuzumab at 0.2 mg/kg for 6 days, with or without TBI at 2 Gy).

For prophylaxis against GVHD, cyclosporine A (CsA) at 3 mg/kg/day or tacrolimus at 0.03 mg/kg/day was combined with short-term methotrexate (10–15 mg/m^2 on Day 1, 7–10 mg/m^2 on Days 3 and 6, and optionally on Day 11). For patients who received graft from an HLA-mismatched donor, alemtuzumab was added to the TBI regimen or the FB regimen at 0.2 mg/kg for 6 days [15]. Methyl-prednisolone (mPSL) or prednisolone (PSL) at 1 or 2 mg/kg was added for patients who developed grade II-IV acute GVHD, whereas PSL at 0.5 mg/kg or more was added for patients who developed extensive chronic GVHD. Prophylaxis against bacterial, fungal, and *Pneumocystis jirovecii* infections consisted of fluconazole, tosufloxacin, and sulfamethoxazole/trimethoprim. Antigenemia-guided pre-emptive therapy against CMV infection was performed as described previously [16].

Diagnosis and treatment of VZV reactivation

The diagnosis of VZV reactivation was established by the presence of characteristic vesicular skin lesion on an erythematous base within dermatome or a generalized cutaneous distribution. Microbiological and/or pathological confirmation was performed only in equivocal cases. Post-herpetic neuralgia was defined as dermatomal pain persisting beyond 1 month after initial presentation of VZV reactivation. VZV reactivation was treated with intravenous acyclovir at 15–30 mg/kg/day in the majority of patients, and followed, in some patients, by oral acyclovir at 1–4 g/day or oral valacyclovir at 3 g/day, for a total treatment period of 5–42 days. A proportion of patients received outpatient treatment only, with valacyclovir 3 g/day orally for 5–10 days. The doses and dosing interval of these drugs were adjusted according to the creatinine clearance in patients with renal impairment.

Prophylactic administration of acyclovir

As prophylaxis against herpes simplex virus infection (HSV), acyclovir was given at 750 mg/day intravenously or at 1,000 mg/day orally from Day 7 to 35. We started long-term oral administration of acyclovir at an ultra-low-dose (200 mg/day) as prophylaxis against VZV reactivation (hereinafter described as "long-term acyclovir") in July 2001, and it was applied for all allogeneic transplantation recipients thereafter. Long-term acyclovir was principally given from Day 36 until the end of immunosuppressive therapy and at least 1 year after HSCT. When intravenous ganciclovir was required for the treatment of CMV infection, acyclovir was discontinued during the course of intravenous ganciclovir

and resumed afterward. In some patients, acyclovir was discontinued within a year or before the cessation of immunosuppressive therapy at the physician's discretion or at the request of patients themselves.

Statistical analysis

The cumulative incidence of VZV reactivation and the impact of possible confounding factors on VZV reactivation were evaluated using Gray's method, considering death without VZV reactivation as a competing risk [17]. The development of acute and chronic GVHD was treated as time-dependent covariates. The influence of chronic GVHD was evaluated only in patients who survived longer than 100 days. Factors associated with at least borderline significance ($P < 0.10$) in univariate analyses were subjected to a multivariate analysis using backward stepwise proportional-hazard modeling. *P*-values of less than 0.05 were considered statistically significant.

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