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Incidence and risk of post-herpetic neuralgia after varicella zoster virus infection in hematopoietic cell transplantation recipients: Hokkaido Hematology Study Group

Running title: PHN after VZV infection in HCT recipients

Masahiro Onozawa[1], Satoshi Hashino[1], Yoshifumi Haseyama[2], Yasuo Hirayama[3], Susumu Iizuka[4], Tadao Ishida[5], Makoto Kaneda[6], Hajime Kobayashi[7], Ryoji Kobayashi[8], Kyuhei Koda[9], Mitsutoshi Kurosawa[10], Nobuo Masauji[11], Takuya Matsunaga[12], Akio Mori[13], Masaya Mukai[14], Mitsufumi Nishio[1], Satoshi Noto[15], Shuichi Ota[16], Hajime Sakai[17], Nobuhiro Suzuki[18], Tohru Takahashi[19], Junji Tanaka[1], Yoshihiro Torimoto[20], Makoto Yoshida[21], Takashi Fukuhara[22]

[1]Stem Cell Transplantation Center, Hokkaido University Graduate School of Medicine, Sapporo, Japan

[2]Department of Hematology, Tonan Hospital, Sapporo, Japan

[3]Department of Internal Medicine, Higashi Sapporo Hospital

[4]Department of Pediatrics, Tenshi hospital, Sapporo, Japan

[5]First Department of Internal Medicine, Sapporo Medical Collage, Sapporo, Japan

[6]Department of Pediatrics, Hokkaido University Graduate School of Medicine, Sapporo, Japan

[7]Forth Department of Internal Medicine, Sapporo, Japan

[8]Department of Pediatrics, Sapporo Hokuyu Hospital, Sapporo, Japan

[9]Department of Hematology and Oncology, Asahikawa Red Cross Hospital, Asahikawa, Japan

[10]Department of Hematology, National Hospital Organization, Hokkaido Cancer Center,

Sapporo, Japan

[11]Department of Internal Medicine, Hakodate Municipal Hospital, Hakodate, Japan

[12]Forth Department of Internal Medicine, Obihiro Kosei Hospital, Obihiro, Japan

[13]Department of Internal Medicine, Aiiku Hospital, Sapporo, Japan

[14]Department of Clinical Immunology and Hematology, Sapporo City General Hospital, Sapporo, Japan

[15]Hakodate Central General Hospital, Hakodate, Japan

[16]Department of Hematology, Sapporo Hokuyu Hospital, Sapporo, Japan

[17]Department of Hematology, Teine Keijinkai Hospital, Sapporo, Japan

[18]Department of Pediatrics, Sapporo Medical Collage, Sapporo, Japan

[19]Department of Hematology, Tenshi Hospital, Sapporo, Japan

[20]Third Department of Internal Medicine, Asahikawa Medical College, Asahikawa, Japan

[21]Department of Pediatrics, Asahikawa Medical Collage, Asahikawa, Japan

[22]Department of Hematology, Asahikawa City Hospital, Asahikwa, Japan

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***Corresponding author:** Masahiro Onozawa, M.D. Department of Gastroenterology and Hematology, Hokkaido University Graduate School of Medicine, Kita-15, Nishi-7, Kita-ku, Sapporo, Hokkaido, JAPAN

ZIP Code : 060-8638

TEL: +81-11-716-1161 (ext. 5920)

FAX: +81-11-706-7867

e-mail address: masahiro.onozawa@nifty.ne.jp

Summary (<200 words) and keywords (3-6)

To assess the incidence of and risk factors associated with post-herpetic neuralgia (PHN) after post-hematopoietic cell transplantation (HCT) varicella-zoster virus (VZV) infection, we conducted a retrospective chart review of 418 consecutive patients who underwent HCT between April 2005 and March 2007. Male/female ratio was 221/197, median age at HCT was 47 years (range, 0-69 years), and autologous/allogeneic/syngeneic HCT ratio was 154/263/1. Seventy-eight patients developed VZV infection after HCT. Sixty-two patients had localized zoster, 11 patients had disseminated zoster (rash like chicken pox), and 4 patients had visceral zoster. All cases were treated with acyclovir (ACV) or valacyclovir (VACV), and there was no VZV infection-related death. Twenty-seven (35%) of the 78 patients with VZV infection suffered PHN after resolution of VZV infection. Multivariate analysis showed that advanced age is the only risk factor in autologous HCT (*P*=0.0075; OR=1.14; 95% CI, 0.97 to 1.33). On the other hand, advanced age (*P*=0.0097; OR=1.06; 95% CI, 1.01 to 1.12), male gender (*P*=0.0055; OR=12.7; 95% CI, 1.61 to 100.1), and GVHD prophylaxis with a tacrolimus-based regimen (*P*=0.0092; OR=9.56; 95% CI, 1.44 to 63.3) were associated with increased risk of PHN in allogeneic HCT. This study for the first time clarified the risk of PHN in HCT recipients.

Keywords: Varicella-zoster virus, post-herpetic neuralgia, disseminated zoster, visceral zoster

Introduction

Reactivation of varicella-zoster virus (VZV) is a common event in patients undergoing hematopoietic cell transplantation (HCT).[1-5] In HCT recipients, VZV reactivation frequently occurs as localized zoster and sometimes as disseminated cutaneous lesions resembling varicella with or without visceral involvement, which results in a high mortality rate. The most common complication associated with zoster in healthy individuals is chronic and often debilitating pain called post-herpetic neuralgia (PHN), which can last for several yeas and may reduce quality of life. Although many previous studies have shown a high incidence of VZV reactivation after HCT, the incidence and risk of PHN in HCT recipients have not yet been clarified.

Patients and Methods

Patients.

To assess the incidence and risk factors associated with PHN after post-HCT VZV infection, we conducted a retrospective chart review of 418 consecutive patients who underwent HCT in Hokkaido Hematology Study Group (HHSG) between April 2005 and March 2007. HHSG is multicentric clinical study group that includes “all” hematology departments in Hokkaido prefecture, consisting of 26 clinical groups of 19 institutes. VZV infection was defined by the appearance of typical cutaneous vesicular lesions or the detection of VZV antigen. Information on pre-transplant therapeutic exposures, HCT procedures and post-transplant health complications was obtained via evaluation form. A total of 418 patients were included in this study. Patients characteristics are summarized in Table 1. Male/Female ratio was 221/197, median age at HCT was 47 years (range, 0-69 years), autologous HCT/allogeneic HCT/syngeneic HCT ratio was 154/263/1, and

median length of follow-up was 344 days (range, 3-1165 days). Short-term (up to 6 weeks) administration of acyclovir (ACV) or valacyclovir (VACV) has been widely used as prophylaxis against herpes simplex virus in Japan. Duration of prophylaxtic ACV or VACV differed in each institution. The current Japanese medical insurance system only covers oral ACV at 1000 mg/day from HCT day -7 to day 35 in allogeneic HCT. In an autologous transplantation setting, duration of prophylaxtic anti-viral drug administration varied from 0 to 239 days (median of 7 days), and in an allogeneic transplantation setting, duration varied from 10 to 189 days (median of 43 days). Duration of prophylaxtic anti-viral drug administration was longer in an allogeneic HCT setting than in an autologous HCT setting (P<0.001).

Diagnosis of clinical VZV infection. VZV infection was defined by the appearance of typical cutaneous vesicular lesions or the detection of VZV antigen. Localized zoster was defined as the presence of vesicular lesions in a dermatomal distribution. Disseminated zoster was defined as a generalized vesicular eruption that is identical to that of varicella. Visceral dissemination was defined as clinical evidence of internal organ involvement in the absence of other identified pathogens that might have accounted for the clinical syndrome. Post-herpetic neuralgia was defined as dermatomal pain that persisted beyond rash healing.

Statistical analysis. The incidence of VZV reactivation was calculated by the Kaplan-Meier method and differences between groups were compared using the log-rank test. We performed univariate analysis for comparisons between different groups of patients or clinical data using the chi square test and *t*-test, as appropriate. We performed

multivariable logistic regression modeling with the forward stepwise method to assess which predictors independently contribute to prediction of PHN and to what extent using odds ratios with 95% CI. All *P*-values were two-sided and a *P*-value of 0.05 was used as a cutoff for statistical significance. Patients who remained free of VZV infection after transplantation were censored at the time of their last follow-up or death from unrelated causes. A case with syngeneic transplantation was dealed with as an autologous transplantation. Analyses were done with Dr.SPSS for Windows (version 8.0.1J).

Results

VZV reactivation

Seventy-eight patients developed VZV infection after HCT (M/F=36/42; median age, 48 (range, 3-68) years; auto/allo/syngeneic=29/48/1). Sixty-two patients had localized zoster (single dermatome in 53, double dermatomes in 9), 11 patients had disseminated zoster (rash like chicken pox), and 4 patients had visceral zoster (involvement of the GI tract). No VZV infection occurred during the period of prophylactic antiviral drug administration. All cases were treated with ACV or VACV, and there was no VZV infection-related death. The incidence of VZV infection in females (21.3%) was slightly higher than that in males (16.7%), but the difference was not statistically significant (*P*=0.22). The incidences of VZV infection were not different between age groups. After resolution of VZV infection, VZV infection reoccurred in 5 cases (localized zoster in 4 cases and visceral zoster in 1 case). Cummulative incidences of VZV infecion in allo-HCT and auto-HCT recipients were estimated to be 34% and 22%, respectively, at 2 years after HCT (Log-rank *P*=0.23) (Figure 1). In autologous HCT, 96.6% of the cases of VZV infection occurred during the first year after HCT, but in allogeneic HCT, only 75.5% of the cases of VZV infection occurred during

the first year after HCT. The cumulative incidences of VZV infection in auto-HCT and allo-HCT recipients were not statistically different because the incidence curves crossed at 1 year after HCT. However, in an autologous setting, prophylactic usage of acyclovir was shorter (0-239 days, median of 7 days) than that in an allogeneic HCT setting (10-189 days, median of 43 days) (P<0.001). Since no VZV infection occurred during the period of prophylactic antiviral drug administration, earlier onset of VZV infection in auto-HCT recipients may be due to the shorter period of prophylactic antiviral drug usage. In an allogeneic setting, the rate of VZV infection in patients who underwent related donor BMT was lower than that in patients who underwent transplantations of stem cells of other sources (Figure 2).

Incidence of PHN

Twenty-seven (35%) of the 78 patients with VZV infection suffered PHN after resolution of VZV infection (M/F=15/12; median age, 56 (range, 21-64) years; auto/allo=13/14). Although incidences of VZV infection were not different between age groups, the incidence of PHN increased with advance of age (Figure 3). Univariate analysis showed advanced age to be a risk factor in both allogeneic HCT and autologous HCT (Table 2). In allogeneic HCT, FK506 usage and GVHD at onset of VZV infection to were shown to be risk factors. There was no significant difference between the incidence of PHN in patients in whom antiviral therapy was initiated within 24 hours of clinical onset (no Tx delay) and that in patients in whom antiviral therapy was initiated after 24 hours from onset (Tx delay). Multivariate analysis showed that advanced age is the only risk factor in autologous HCT (P=0.0075; OR=1.14; 95% CI, 0.97 to 1.33). On the other hand, advanced age (P=0.0097; OR=1.06; 95% CI, 1.01 to 1.12), male gender (P=0.0055; OR=12.7; 95% CI, 1.61 to 100.1),

and GVHD prophylaxis with a tacrolimus-based regimen (*P*=0.0092; OR=9.56; 95% CI, 1.44 to 63.3) were associated with increased risk of PHN in allogeneic HCT. Results of statistical analysis between autologous vs allogeneic HCT (data not shown), onset of VZV infection after HCT, gammaglobulin usage, localization of rash, CST vs RIST, stem cell source, and GVHD at onset of VZV infection were not significant.

Discussion

Herpes zoster after hematopoietic cell transplantation

Reactivation of latent VZV, presenting as localized zoster or as disseminated infection, is a common and potentially serious complication in HSCT recipients. Previous studies revealed that 23% to 60% of patients could be expected to develop VZV infection after HSCT.[1-4] Analyses of risk factors such as allogeneic versus autologous transplant, graft-versus-host disease (GVHD), underlying disease, and pre-BMT irradiation have not revealed definitive associations.[1,2] In our study, age, gender, CST vs RIST, and total body irradiation did not show a definitive association with VZV infection after HCT. Tomonari *et al*. reported a high risk of VZV infection after cord blood transplantation (CBT).[6] In our series, CBT a similar risk of VZV infection similar to that of other stem cell sources except related bone marrow, which showed a lower risk.

Cutaneous and visceral dissemination

VZV infection after HCT sometimes progressed to systemic infection. In previous series, 2-20% of the cases of VZV infection were disseminated zoster and 3-5% of cases were visceral dissemination such as acute abdomen, pneumonitis and CNS involvement.[1] Risk of disseminated disease has not been studied in detail. Previously, we showed an

association of pre-existing (before onset of VZV infection) anti-VZV IgG titer and disseminated VZV infection.[5] In our previous observations, herpes zoster occurred despite prolonged existence of anti-VZV IgG after HCT. Recipients with lower pre-existing VZV-IgG titer had higher viral copies in their serum at onset of VZV infection and tended to present as a disseminated disease. It is well known that cell-mediated immunity to VZV is a major determinant of the risk and severity of herpes zoster; however, decreasing humoral immunity after HCT might contribute to disseminated VZV infection.

Second episodes of herpes zoster

Five patients (one autologous HCT recipient, 4 allogeneic HCT recipients) developed two episodes of VZV infection after HCT. The average interval between episodes was 9 months (range, 2 to 31 months). Four recipients had recurrence as localized zoster and 1 recipient had recurrence as visceral zoster (esophageal involvement). Two of the five patients with multiple VZV infection suffered PHN. In immunocompetent individuals, a second episode after resolution of zoster is quite unusual, but HCT recipients sometimes have plural episodes of VZV infection, indicating the failure to reconstitute VZV specific immunity due to prolonged insufficient immunity.[1]

Postherpetic neuralgia (PHN)

PHN is the most common complication of herpes zoster in immunocompetent as well as immunocompromised patients. Many patients develop severe physical and social disabilities as a consequence of their unceasing pain. Because the effect of treatment is disappointing once the syndrome has occurred, the importance of PHN-preventive strategies is widely recognized. HCT recipients apparently seemed to be at higher risk of

PHN. Locksley *et al.* observed PHN in 25% of HCT recipients, a much higher incidence than the expected incidence of about 9% in healthy individuals.[7] Koc *et al*. reported that PHN and peripheral neuropathy occurred in 43% of HCT recipients.[8] There has been no report in which prevalence and precise risk of PHN after VZV infection in HCT recipients was described. Previous studies in immunocompetent individuals showed that, advanced age, acute pain severity, presence of severe rash, rash duration before consultation, greater degree of sensory impairment, ophthalmic location and psychological distress were potential predictors of PHN.[9,10] Advanced age is the strongest risk factor in immunocompetent adults.[11] The incidence of PNH was reported to be much higher in immunocompetent patients over 60 years old.[11] In HCT recipients, the incidence of PHN was higher at a younger age than that in healthy individuals. This study for the first time clarified the risk of PHN in HCT recipients. The incidence of PHN in HCT patients of a younger age (age>20yrs) was higher than that in healthy individuals. Previous observations support the belief that a decline in cell-mediated immunity to VZV can lead to a higher incidence and greater severity of herpes zoster and post-herpetic neuralgia.[12] Due to severe cellular immunoincompetence, the risk of PHN is considered to be high in HCT recipients. In our series, the incidences of VZV infection were not significantly different in males and females, but the incidence of PNH was higher in males only in allogeneic HCT recipients. The effect of gender on risk of herpes zoster or PHN is controversial.[11]

Prophylaxis

In our series, immediate antiviral drug administration did not reduce the incidence of PHN. A previous study in immunocompetent individuals showed that antiviral therapy reduced the

severity and duration of herpes zoster but did not prevent the development of PHN.[13] One factor potentially limiting the effect of antiviral agents on chronic pain is the fact that VZV replication occurs for several days or weeks before a rash appears and a diagnosis can be made. Therefore, to prevent PHN, we should prevent VZV reactivation itself. Some studies have shown successful long-term usage of ACV for prophylaxis of VZV infection after HCT. Administration of ACV for a period as long as that immunosuppressant usage and at least 1 year after HCT even at a low dose (ACV 200-400 mg daily) successfully reduced the incidence of VZV reactivation at 1 year after HCT, but VZV reactivation after cessation of ACV administration was still high (29-32.1%).[14,15] Another study showed that subclinical reactivation was important to reconstitute donor-derived VZV-specific immunity.[16] 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.[16] Therefore, administration of ACV suppresses VZV reactivation but at the same time might also suppress recovery of VZV-specific immunity by preventing contact of immune cells with VZV antigen. Active immunization by a vaccine is theoretically reasonable; however, the current VZV vaccine used worldwide is a live attenuated vaccine and therefore cannot be used in HCT recipients for a period within 2 years after transplantation.[17] Inactivated varicella vaccine may be useful for the early reconstitution of adaptive immunity to VZV after HCT.[1,18] A live attenuated vaccine does not work during anti-viral drug usage, but inactivated vaccine can be administered during prophylaxtic anti-viral drug usage. Therefore, one possible approach is to administer an inactivated VZV vaccine before the discontinuation of prophylaxtic anti-viral drug administration. Appropriate duration of administration and dose of a prophylaxtic anti-viral drug and appropriate timing of inactivated VZV vaccine administration must be studied prospectively.

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of hematopoietic-cell transplants. N Engl J Med 2002; 347:26-34.

Figure legends

Table 1. Patients' characteristics.

Table 2. Risk factors of post-herpetic neuralgia.

Figure 1. Incidence of VZV infection after HSCT (auto vs allo).

Figure 2. Incidence of VZV infection after HSCT (stem cell source).

Figure 3.

(A) Incidence of VZV infection after HCT.

(B) Incidence of PHN after VZV infection.

Table1

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Table 1 Patients' characteristics

Male / Female:		222 / 197
Age (Median):		0-69 (47)
VZV infection (+) / (-):		79 / 340
Hematological disease:		
	Acute myeloblastic leukemia	93
	Acute lymphoblastic leukemia	48
	Myeldysplastic syndrome	30
	Chronic myelocytic leukemia	10
	Non-Hodgkin's lymphoma	115
	Severe aplastic anemia	14
	Hodgkin's lymphoma	10
	Multiple myeloma	46
	Plasma cell dyscrasia	8
	Congental disease	7
	Solid tumor	17
	Adult T-cell leukemia	6
	Screloderma	5
	Myeloproliferative disease	5
	Juvenile myelomonocytic leuekmia	3
	Chronic lymphocytic leukemia	1
	Chronic neutrophilic leukemia	1
Stem cell source:		
auto PBSCT		154
allogeneic		264
	related BMT	38
	related PBSCT	55
	related CBT	2
	unrelated BMT	96
	unrelated CBT	73
syngeneic		1
Preparative regimen in allo-HCT		
	CST/RIST:	147 / 117

Table2

Table 2. Risk factors of post-herpetic neuralgia

	Autologous HCT (n=30)					Allogeneic HCT (n=48)		
	no PHN (n=17)	PHN (n=13)	Univariate	Multivariate		no PHN (n=35)	PHN (n=13)	Univariate
			P value	Odds ratio (95% CI)	*P* value			*P* value
Male/Female	9/8	7/6	0.96			12/23	8/5	0.089
Age (median)	8-61 (49)	44-64 (57)	0.00023	1.14 (0.97-1.33)	0.0075	3-68 (38)	25-60 (48)	0.028
Onset of VZV infection after HCT								
<1year / >1year	16/1	13/0	0.37			27/8	9/4	0.57
Delay of ACV administration								
no Tx delay / Tx delay	7/9	7/5	0.45			14/21	7/6	0.39
Gammaglobulin usage (-) / (+)	8/5	8/4	0.79			18/10	9/4	0.76
Localization of rash								
Including face / no facial lesion	6/9	2/11	0.15			8/26	4/9	0.61
CST / RIST	-	-	-	-	-	18/17	6/7	0.75
Allogeneic stem cell source								
uBM/rBM/rPB/CB*	-	-	-	-	-	14/3/6/12	7/0/4/2	0.32
GVHD prophylaxis CyA base / FK base*	-	-	-	-	-	22/13	4/9	0.047
GVHD at onset of VZV infection (-) / (+)	-	-	-	-	-	18/17	3/10	0.078

*uBM: unrelated bone marrow, rBM: related bone marrow, rPB: related peripheral blood, CB: cord blood, CyA: cyclosporin A, FK: tacrolimus

Multivariate	
Odds ratio (95% CI)	*P* value
12.7 (1.62-100.1)	0.0055
1.06 (1.01-1.12)	0.0097
9.56 (1.44-63.3)	0.0092

Figure1
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Figure 1. Incidence of VZV infection after HCT (auto vs allo).

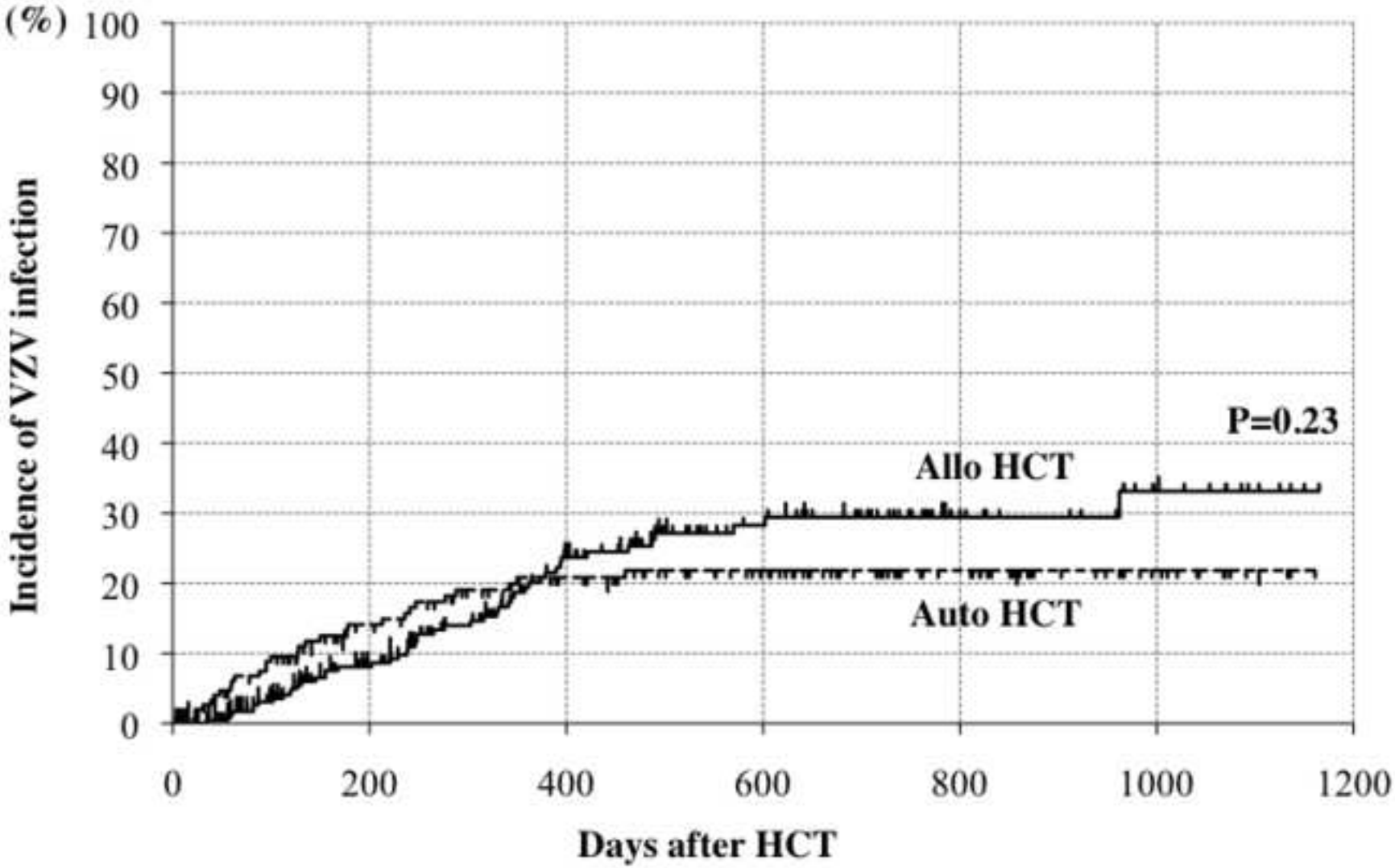


Figure2
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Figure 2. Incidence of VZV infection after HCT (stem cell type).

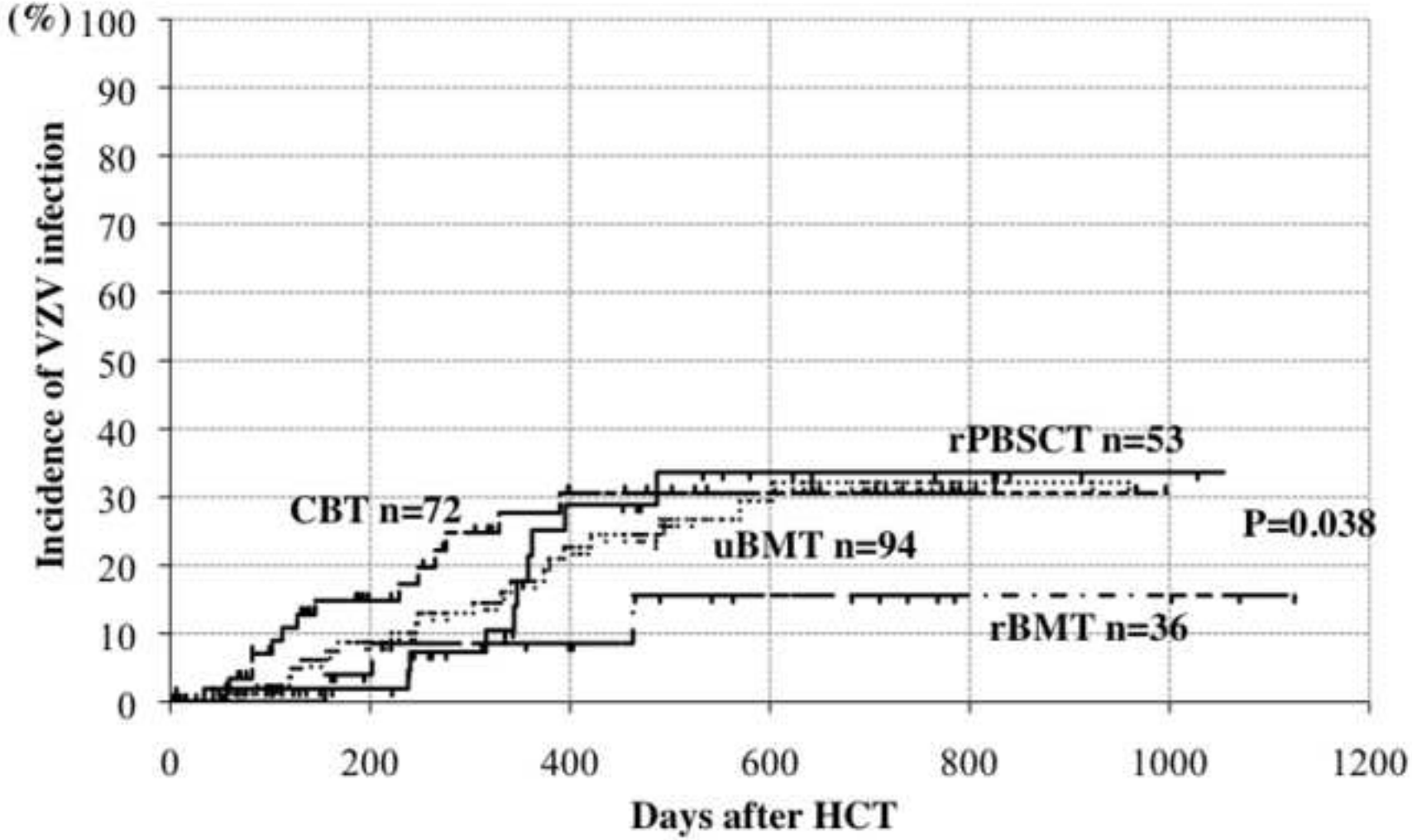


Figure3
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Figure 3. Incidence of VZV infection and PHN in each generation.

