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Incidence and Risk of Postherpetic Neuralgia after Varicella Zoster Virus Infection in Hematopoietic Cell Transplantation Recipients: Hokkaido Hematology Study Group

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To assess the incidence of and risk factors associated with postherpetic neuralgia (PHN) after 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. The 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 ($P = .0075$; odds ratio [OR] = 1.14; 95% confidence interval [CI], 0.97-1.33). On the other hand, advanced age ($P = .0097$; OR = 1.06; 95% CI, 1.01-1.12), male gender ($P = .0055$; OR = 12.7; 95% CI, 1.61-100.1), and graft-versus-host disease (GVHD) prophylaxis with a tacrolimus-based regimen ($P = .0092$; OR = 9.56; 95% CI, 1.44-63.3) were associated with increased risk of PHN in allogeneic HCT. This study for the first time clarified the risk of PHN in HCT recipients.

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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 postherpetic 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 a 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 the VZV antigen. Information on pretransplant therapeutic exposures, HCT procedures, and posttransplant 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 (HSV) in Japan. Duration of prophylactic 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 prophylactic antiviral 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 prophylactic antiviral drug administration was longer in an allogeneic HCT setting than in an autologous HCT setting ($P < .001$).

Table 1. Patients' Characteristics.

Male/Female:	221/197
Age (Median):	0-69/(47)
VZV Infection (+)/(-):	78/340
Hemotologica Disease:	
Acute Myelogenous leukemia	93
Acute Lymphoblastic leukemia	48
Myelodysplastic syndrome	30
Chronic myelogenous leukemia	10
Non-Hodgkin lymphoma	115
Severe aplastic anemia	14
Hodgkin lymphoma	10
Multiple myeloma	46
Plasma cell dyscrasia	8
Congenital disease	7
Solid tumor	17
Adult T cell leukemia	5
Secreloderma	5
Myeloproliferative disease	5
Juvenile myelomonocytic leukemia	3
Chronic lymphocytic leukemia	1
Chronic neutrophilic leukemia	1
Stem cell source:	
auto PBSCT	154
allogeneic	263
related BMT	38
related PBSCT	55
related CBT	2
unrelated BMT	95
unrelated CBT	73
syngeneic	1
Preparative regimen in allo- HCT	
CST/RIST	146/117

PBSCT indicates peripheral blood stem cell transplantation; CST, conventional stem cell transplantation; RIST, reduced intensity stem cell transplantation; CBT cord blood transplantation; BMT bone marrow transplantation; HCT, hematopoietic cell transplantation; VZV, varicella zoster virus

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. PHN 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%